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Original Communications

THE NEWER GYNECOLOGY*

BY BARTON COOKE HIRST, M.D., PHILADELPHIA, PA.

I CANNOT refrain from expressing my profound appreciation of the kindness of my fellow-members in conferring on me the highest honor of my professional life; a kindness appreciated all the more because I know that many of the members by their loyalty to the Society and their numerous valuable contributions to its transactions are far more worthy of this distinction than I am.

If the custom of the Presidential address is to continue, it should justify itself for robbing the meeting of time that could more profitably be devoted to the scientific programme, by suggestions to further the interests of the Society.

Every existence, be it individual or corporate, shows progression or retrogression. The direction it shall take is determined by qualities inherent in itself or by its environment. The distinguished character of our membership should assure progress, but we are not absolutely secure against the pitfalls that beset the path of every career, and there is much that is disquieting in our political and social environment.

A transplanted and isolated civilization tends to deteriorate. The far distant Grecian colonies to which their founders carried the sacred fire from the public hearth never equaled the glory that was Greece's. Our isolation was accentuated by the violent rupture with the chief source of our culture—Great Britain—in the American Revolution. In consequence we have developed to a greater degree than should be the case in a commonwealth politically and socially sound, traits of

*The President's Address read before the forty-ninth annual meeting of the American Gynecological Society, Hot Springs, Va., May 15 to 17, 1924.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

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national character difficult to define by a single word, but best described perhaps as provincial: Ignorance of the rest of the world and of the customs of civilized society, intolerance, overweening self-esteem; a distorted sense of proportion; resentment of foreign criticism, indifference to the lessons of history; insensibility to the inspiration of art, music, literature, to whatever contributes to the joy of living and the attainment of happiness and a disposition to try bizarre experiments in education, legislation and government. We present at present the remarkable spectacle of a people supposed to possess intelligence and political capacity, incorporating in the basic law of the state a mere sumptuary regulation and attempting to enforce it by squandering the public funds, by invading the rights of the individual in a manner not tolerated by English-speaking people since the days of the Stuarts; and by letting loose on the community a horde of spies, provocative agents and disreputable officials "in whose hands is mischief and their right hand is full of bribes." Such an attempt has never succeeded in the whole history of human government and never will.

An inevitable result of ill-considered, impracticable, unenforcible, unnecessary laws is a contempt, not only for all law, but for the law makers who set the first example of disobedience to their own laws. The legislative branch of the Government stands highest in the reverence of a well-governed people; the executive and judicial branches simply administering and interpreting the law. If by their ineptitude, lack of character and intelligence the legislators convert the reverence of the people to a feeling quite the reverse, they commit the nation to its first step toward anarchy or a dictatorship.

Unfortunately we cannot echo Mme. du Deffand's comment on the story of the martyrdom of St. Denis, by Cardinal de Polignac, that in such a situation it is only the first step that counts. Where will this first step lead us? St. Denis, with his gory head in his hands, staggering along the six miles from Mont Martre to the site of his future church, had at least a definite destination. But what of ours? Strangely enough we appear to be moving in two directions at the same time. Contrast our respect for the Presidency with our opinion of Congress. There is a drift toward autocracy, while the prevalence of crimes of violence in the United States, unparalleled in any other English-speaking country shows a drift toward anarchy. Since we convened this morning four people have been murdered and another is being done to death as I speak, for with fourteen thousand six hundred and forty unjustifiable homicides in a single year in the United States, someone somewhere is being murdered every thirty-five minutes and probably with impunity, for in these crimes of violence in this country, the criminal is rarely apprehended and still more rarely punished. There was a time when the quality of our population justi-

fied supreme confidence in the future, no matter what temporary vagaries were to be deplored, but with the neglect of selective immigration, we have fourteen million people of foreign birth, one and a half times that number of foreign parentage, not to mention twelve million negroes, most of whom have never known self-government and are incapable of exercising it.

In moments of discouragement at the prospect of our political future, we cannot help recalling the statement of Tacitus that "it is easier to praise a republican form of government than to establish it, and when it is established it cannot be of long duration" and wondering if we are to add another to the numerous verifications of this prediction afforded by the past twenty centuries.

This is not the time nor the place to analyze our social state and besides it has already been done in recent fiction, showing with photographic accuracy a cross section of American life, too often a drab, monotonous, futile thing, or a mad pursuit of mere pleasure, devoid of grace, dignity, wit, lightheartedness, joyousness, gayety, of everything that makes life worth while and this too, not among the dregs of the population but among the well-to-do with means to make of their lives all that they might be if these people had not lost the knowledge of how it could be done.

He who lacks the inclination to read this fiction, might look in the mirror held up to us by Langdon Mitchell in his *Diagnosis of Our National Temperament*. He will see a picture of a people losing its grip on the civilization transplanted to this continent from Europe and replacing it by a culture which we can only hope will not prove inferior; a picture all the more startling for the good humor, tolerance and lack of pessimism with which it is presented.

It might well be asked what these desultory thoughts on government and civilization have to do with our Society and its work. Let the oracular Captain Bunsby reply: "The bearings of this observation lays in the application on it." Could we escape the insidious influence on our scientific work, of defects in our political and social environment unless we recognized and avoided them?

There is a tiny cloud on the horizon that might dim the radiance of a brilliant past, if it ever reached much larger dimensions, a thought suggested by the shrinkage not in the quality but in the size of our transactions.

Yielding to the weakness of resting on our laurels, we might relax the efforts which have made us what we are, till we become the mere "shadow of a mighty name" or what is more appropriate to us than Lucan's reference to Pompey, entrance in this Society with its history, achievements, prestige and traditions, might engender in some of us a frame of mind comparable with that of the ancient Greeks who believed they could acquire medical knowledge and skill by

simply sleeping in the Aesculapian Shrines at Epidaurus, the reputed birthplace of the Father of Medicine.

We might stray into an error incidental to our special work. Let the feminist say what she will, the male dominates the female throughout Nature. Dealing with women alone as patients there is noticeable in some of us gynecologists an autocratic manner, an inclination to individualistic thought and practice contrary to the cooperative trend of modern medicine. Enough, however, of "Gorgons and Hydras and Chimaeras dire." Enough of a Cassandra's rôle.

It is pleasanter to contemplate our future achievements, greater, I am convinced, even than those of the past, but taking a different direction.

We will have a juster sense of proportion in assigning their relative importance to the subjects within the scope of our specialty.

The title of our Society being what it is and meaning what it does, a study of woman, the chief act of her life, the reason for her creation and existence, the act of reproduction, must be our chief concern. And what function in the whole realm of medicine has greater importance to the individual, the family and the State than the successful conduct of a childbirth, a fact recognized by Louis XIV when he ennobled Clément on appointing him accoucheur to Mme. La Vallière.

It is not strange that so much space in our Transactions has been devoted to surgical technic. Coincident almost with the origin of this Society was the birth of modern operative gynecology. For the first time in the history of mankind many painful, dangerous and fatal affections in women became amenable to surgical treatment. The men who blazed the way to these discoveries have a rightful place among the great figures of medicine. The inclusion of some of the most distinguished among them in the membership of this Society gave it a lustre outshining its sister special societies and commanding for its transactions the admiration and attention of the whole medical profession. But that day is passed. We have learned our lesson and what is more, have taught it to others. To keep harping on this twice-told tale is to deserve the taunt of the general surgeon that our specialty is no longer necessary. No one can be an expert in the treatment of all the diseases peculiar to women who is not an accomplished pelvic and abdominal surgeon, but he must be something more. He must study all the diseases of women in close correlation with the chief act of a woman's life and must be equally able to deal with the act of reproduction in all its phases, as well as with all the diseases that follow or complicate it. With such knowledge he need fear the rivalry of no general surgeon. Without it he is either a supermidwife or a surgeon of limited ability and experience.

With this broad outlook on our subject there is a fascinating field for future advancement and improvement.

The education of medical students, our successors, according to this modern concept, recognized now everywhere to be correct, should, I think, receive more attention from our members than it has in the past. To whom is the general public, the trustees and faculties of our medical schools to look for advice on this important subject if not to the members of this Society, admittedly containing the most prominent teachers of this branch of medicine in the country. In the humble opinion of an individual member, we should have a standing committee on education in constant communication with the Association of American Medical Colleges, with the Council on Medical Education of the American Medical Association and with the boards of Licensure of the nation and of the several states; and be it said, *sotto voce*, among ourselves, ours should be the prevailing voice in this association in everything pertaining to medical education and requirements in our special subject.

It would be a presumption in a single member to enumerate the possibilities of the future for investigation and discovery, even if he could forsee them all. But there are some problems in the minds not only of ourselves but of the general public that should obviously engage our attention. Among them is the discovery of some method to mitigate the pains of childbirth with safety to the mother and child and practicable for the general physician in private practice. Dr. Gwathmey's recent proposition points one way in this direction I believe, after a personal test of it.

What shall be our attitude toward birth control, a matter in the minds of all of us, physician and layman alike, but about which we seem unwilling to express an opinion? Should we take the leadership in this matter instead of resigning it to people without knowledge of all that it involves? Or should we deliberately and publicly decline to do so, restricting our communication of the knowledge we possess to individual patients at our discretion?

We need not agree with Pope that every woman is at heart a rake, to admit that the fear of pregnancy keeps some women chaste who otherwise might not be so. Are we willing to give authoritative public advice that would remove this deterrent influence? And who is to limit the limitation of fecundity? I have been told of a hamlet in Connecticut of some eight hundred inhabitants containing the typical New England school house. The school has one pupil, a little girl eight years old. When she graduates the school must be closed for there is not another child in sight. Dare we aid in the creation of a Frankenstein that may depopulate the State?

We have an opportunity for an altruistic achievement which no other branch of medicine presents. Fifty-one per cent of women who consult physicians on account of something peculiar to their sex have injured birth canals; 10 per cent have retroversion. We have it in

our power to teach the profession how these conditions can be prevented or immediately cured, thus wiping out 60 per cent of all the diseases of women.

The infections of the puerperium must be studied till we can control them. There has been a strange neglect of this important subject. It was amazing to find so little constructive suggestion in answer to a questionnaire recently sent to many maternities. Chemical disinfection of the blood should be investigated further; a larger intravenous dose of a specific serum than has hitherto been given, as suggested in the Congress at Strasburg last summer, is worth a trial.

Can we not find an antitoxin to the toxins of streptococcaemia? Should we not consider the propriety of using radium in malignant growths always in association with an expert radiologist who has an equipment for the different forms of radiation we could not employ if we had it and without which the patient is not given all the aid this agent might afford her?

The toxemias of pregnancy still await elucidation, and their most successful treatment, standardization.

That most forlorn among a doctor's patients, the sterile wife, should look to us for added knowledge that will give her hope in her pathetic yearning for maternity.

Endocrinology has in store for us discoveries more startling than those already made. To the next generation what we would think marvelous results of hormonic treatment will be commonplace. Of this, as of every subject we investigate, a second Cicero could say again with equal truth that posterity will wonder we could be ignorant of things so evident.

The illimitable prospect before us tempts one so far afield that if I wandered farther your patience would be overtaxed. The vision of the age to come so stirs the blood it is difficult to speak with becoming restraint.

There are moments of exaltation in our lives when, at an inspiring thought, the recountal of a noble deed, a touch of genius in art, a glimpse of transcendent beauty in nature, the spark of divinity in us all, bursts into a brighter flame; our cloak of mortality drops partly from us and we look into the future,

> "As if the mental eye gained power to gaze
> Beyond the limits of the existing world."

In such a mood I see our Society and others like it, sharing the triumphs of their sister medical and surgical associations in the mastery of suffering and disease and in the effort to prolong the span of life; but above all, a privilege all our own, superintending the reproduction, the perpetuation and the improvement of the human race from generation to generation.

1821 Spruce Street.

THE SERUM TREATMENT OF PUERPERAL SEPSIS*

By Harold Bailey, M.D., F.A.C.S., New York, N. Y.

(*Continued from page 658, June issue.*)

REPORT OF CASES

Group I.—Cases in which the Intrauterine Culture Showed Streptococcus Hemolyticus.

1. M. S., para iii; a case from the prenatal clinic. She was admitted to Bellevue Hospital on April 1, 1923, and discharged on May 10. There were no rectal or vaginal examinations and the delivery was spontaneous. A loop of cord about the neck was slipped over the child's head during delivery.

On the fourth day there was a chill and rise in temperature to 103° with a continued fever ranging between 103° and 104° through several days. The leucocyte count on April 7 was 17,600 with 91 per cent polynuclear cells. A culture was taken from within the uterus and reported as streptococcus hemolyticus. One hundred c.c. of serum was given on the eighth, ninth, eleventh, twelfth and fourteenth days with very little change in the temperature curve. On the fourteenth day the temperature dropped to 102° and reached normal on the seventeenth day. The leucocytes varied from 16,000 to 18,000 until the seventeenth day when they were 25,800 with 80 per cent polynuclear cells. On the ninth day of the puerperium, when the second dose of serum was given, the patient was prostrated and had a distended and tympanitic abdomen and it was evident that there was some peritoneal inflammation. The blood culture was sterile. There was a slight tenderness in the region of the right parametrium throughout the course of the fever. Recovery appeared to be complete and she was discharged on the fortieth day. (Fig 1.)

2. E. F., para i, aged twenty-two; a case from the prenatal clinic. She was admitted to Bellevue Hospital on March 11 and discharged on April 4. The Wassermann was negative. The patient was in labor with the head in the right occiput posterior position and was delivered by forceps. The perineum was lacerated and repaired. The patient at once showed considerable shock and was given 1000 c.c. saline solution by hypodermoclysis.

On the third day the temperature reached 100.6° and then there was a gradual rise to 104° on the eighth day. On this day the intrauterine culture was taken and reported positive for streptococcus hemolyticus. The blood culture was sterile. Following the administration of 100 c.c. of serum on the tenth day there was a marked reaction and rise in temperature to 106.8°. The following day the temperature was 105° with a pulse of 165. From then on there was a gradual drop by lysis with the temperature reaching normal on the sixteenth day and remaining so until discharge. (Fig 2.)

At the time of the intrauterine culture, leucocytes were 37,000 with 92 per cent polynuclear cells. It is probable that this patient had considerable antibody in her blood and that the additional amount furnished by the serum was sufficient to enable her to recover.

3. O. G., para i, aged eighteen; a case from the prenatal clinic. She was admitted on April 4, 1922, and discharged on April 27. There were no rectal or vaginal examinations and the delivery was spontaneous. The perineum was intact.

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*Read at a meeting of the New York Obstetrical Society, January 8, 1924.

The temperature rose to 102° on the third day and to 103° on the fourth day remaining as a continued fever until the sixteenth day. The leucocytes were 16,000 with 86 per cent polynuclear cells. One hundred c.c. of serum was given on the seventh day and also on the ninth and eleventh days of the postpartum period. The intrauterine culture was taken on the day of the first injection of serum and showed streptococcus hemolyticus. On the sixteenth day the temperature reached normal and remained there. (Fig. 3.)

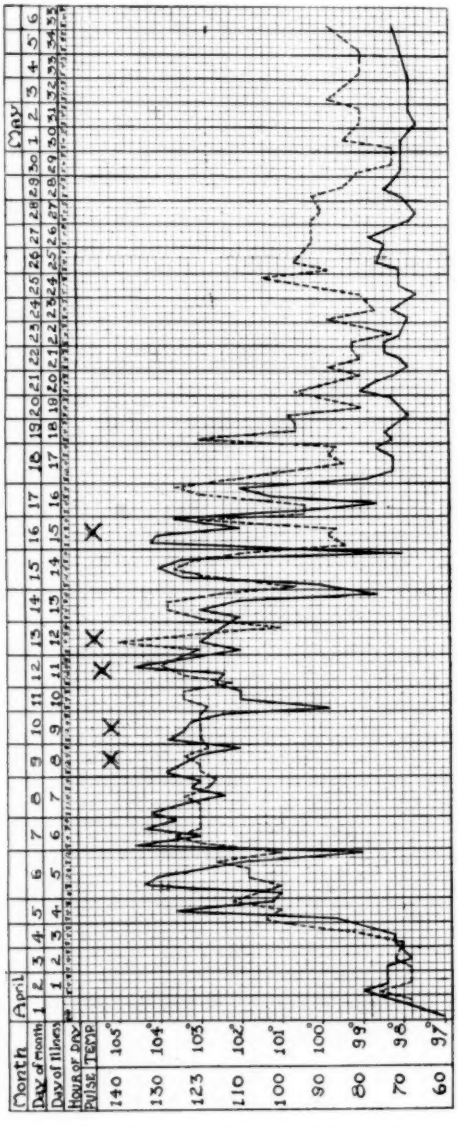

Fig. 1.

4. A. C., para viii; a case from the prenatal clinic. She was admitted to Bellevue Hospital February 23, 1922, and discharged on March 9. She was in the second stage of labor with the membranes presenting. There were no rectal or vaginal examinations and the delivery was spontaneous.

The temperature rose during the night of the third day and reached 103.8° on the fourth day. On this day the leucocytes were 7400 with 77 per cent polynuclear cells. On the third day of the fever the blood culture was sterile. The intrauterine culture showed streptococcus hemolyticus. Fifty c.c. of serum was administered on the sixth day and the temperature did not rise above 101.8°. The next few days it fluctuated below 101°, gradually reaching normal on the 13th day. (Fig. 4.)

5. A. B., para i; aged nineteen; a case from the prenatal clinic. She was admitted to Bellevue Hospital on March 6, 1922, and discharged on the sixty-first day. No rectal or vaginal examinations were made during the labor and the delivery was spontaneous.

On the fourth day the temperature rose to 102.8° and remained as a continued fever fluctuating above 103°. On the third day of the fever the blood culture was taken and reported as negative. The intrauterine culture showed streptococcus hemolyticus. The leucocytes, at the height of the fever, were 14,200 with 85 per cent polynuclear cells. On the seventh day postpartum 100 c.c. of serum was given

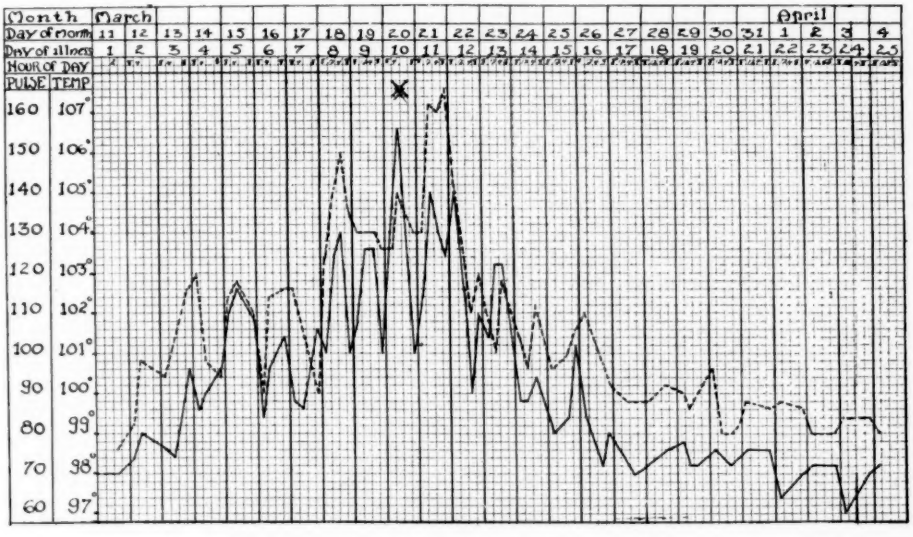

Fig. 2.

and there was a marked reaction, the temperature going to 106°. There was some urticaria, so that although on the following day the temperature was 105°, no serum was given because of the possible dangers of anaphylaxis. Two days later another 100 c.c. was given and was immediately followed by edema of the larynx so that the patient had to be watched for twelve hours. There were fluctuations in the temperature but it gradually reached normal on the eleventh day. (Fig. 5-*A* and *B*.)

On the ninth day this patient had evidences of serum sickness in the swelling of all her joints; her knees especially were affected and were acutely tender. There was a period from the sixteenth to the twenty-third day when the temperature fluctuated below 101.1° and during this period a mass developed in the right parametrium and extended well above the brim of the false pelvis. On the twenty-fifth day the temperature reached 103° and then fluctuated during a period of 8 or 9 days. A transfusion of 50 c.c. of blood was made on the thirty-third day and the thirty-sixth day and there was a gradual improvement, the temperature reaching normal on the forty-eighth day; the mass gradually subsided. This patient is again pregnant and in our care.

6. M. M., para v, aged twenty-seven; a case from the prenatal clinic. She was admitted to Bellevue Hospital on April 11th and died there April 30, 1922. This patient was admitted in labor. There were no rectal or vaginal examinations and the delivery was spontaneous. A loop of cord about the neck of the child was slipped over its head during the delivery.

The temperature rose on the third day to 101.6° and remained as a continued

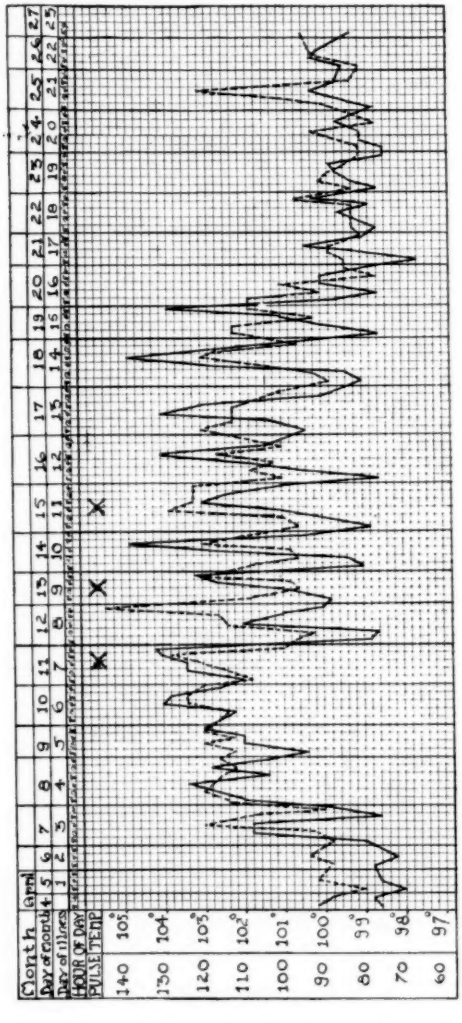

Fig. 3.

fever until the death of the patient on the nineteenth day. After the first three days of fever there were fluctuations in the temperature curve which seemed to indicate that the patient was about to recover spontaneously. However, it rose again to 104° on the ninth day and on the tenth day of the postpartum period 100 c.c. of serum was administered. At this time the leucocytes were 10,500 with 80 per cent polynuclear cells. The intrauterine culture showed streptococcus hemolyticus. On the thirteenth day another injection of 50 c.c. was administered. The patient was exceedingly ill with the abdomen distended and tympanitic. There were signs

in the right chest that pointed to an embolism. At the time of the second injection, the administration had to be stopped because of the effect on the pulse and respiration. The serum had a different laboratory number from that which we had been using for the other cases but it must be admitted that a very insufficient dose was given late in the disease and apparently the organism was a virulent one. Death occurred on the nineteenth day. (Fig. 6.)

Group II.—Eight cases (6 from Bellevue Hospital and 2 from the Bellevue School for Midwives) in which the Blood Culture was Negative and the Intrauterine Culture was Either Negative or not Taken.

1. R. B., para ii, aged twenty-one; a case from the prenatal clinic. She was admitted to Bellevue Hospital on May 15, 1922. This patient had preeclampsia with 3-plus albumin and a blood pressure of 166. The Wassermann was negative. She went into labor on the day following her admission and was delivered by low forceps. No rectal or vaginal examinations were made until the patient was prepared for the operation.

Her temperature 102.4° on the morning of the fourth day and there was a con-

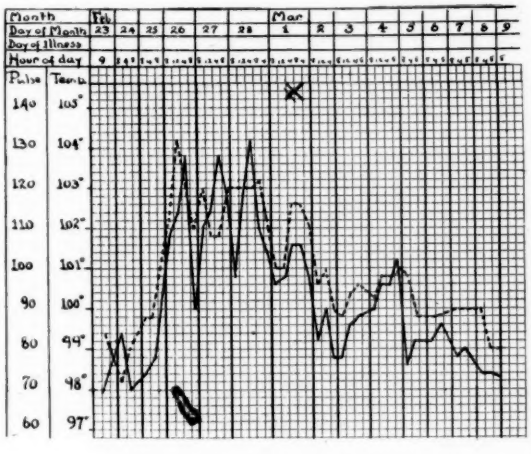

Fig. 4.

tinued fever until the eleventh day. The intrauterine culture was taken, but the report was not noted in the history. On the 3rd day the leucocytes were 14,000 with 86 per cent polynuclear cells. On the sixth and eighth days postpartum 100 c.c. of serum was given. Following the second dose there was a drop in temperature. The blood culture was negative. There was a marked parametritis on the right side. On the twentieth day the temperature rose again to 104° and on the twenty-fifth day with a temperature of 103° and a pulse of 120 she went home against advice. (Fig. 7.)

A short time later she was admitted to the New York Hospital where the cul-de-sac was drained and she recovered.

This patient had a marked serum reaction with urticaria and swelling of the knees and phalangeal joints. Because of this reaction a third dose of serum could not be administered.

2. C. W., para ii, age twenty-nine. This case had had no prenatal care. She was admitted to Bellevue Hospital on April 18, 1922. She was in labor and had a precipitate delivery. No rectal or vaginal examinations were made.

On the second day of the puerperium the temperature reached 103.8° and remained

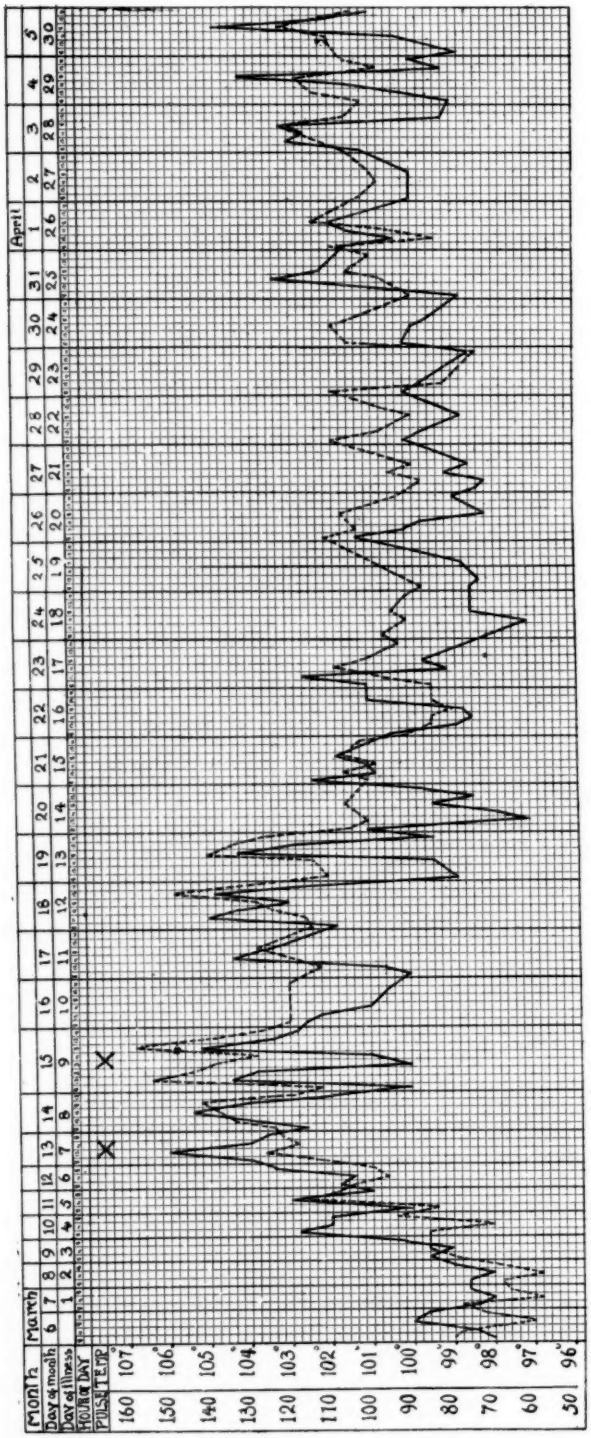
Month
March
April
Day of month
Day of illness
HOUR DAY
PULS. TEMP.

Fig. 5-A.

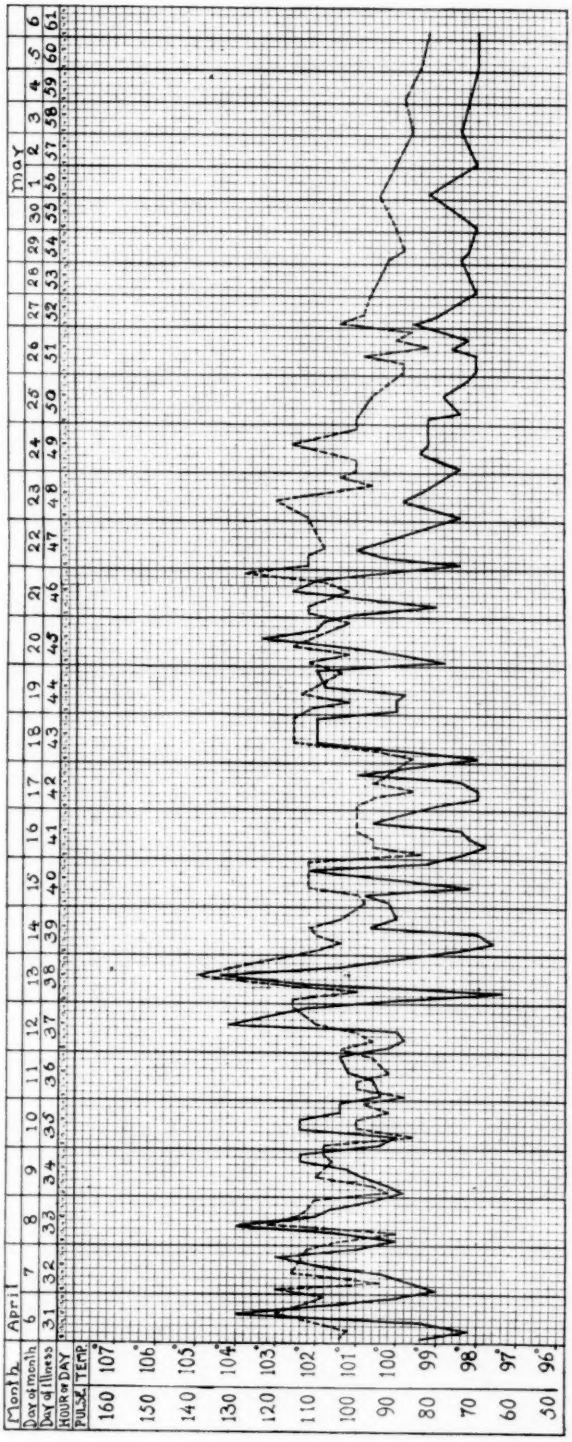
Month
April
May
Day of month
Day of Illness
HOUR of DAY
PULSE
TEMP.
160
150
140
130
120
110
100
90
80
70
60
50
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°

Fig. 5-*B*.

as a continued fever until the thirteenth day. The blood culture was taken on the tenth day and was reported as negative. The leucocytes were 24,000 with 86 per cent polynuclear cells. The intrauterine culture was not taken. On the tenth day of the fever 75 c.c. of serum was given. An almost immediate reaction necessitated the discontinuance of the injection at that amount. On the thirteenth day

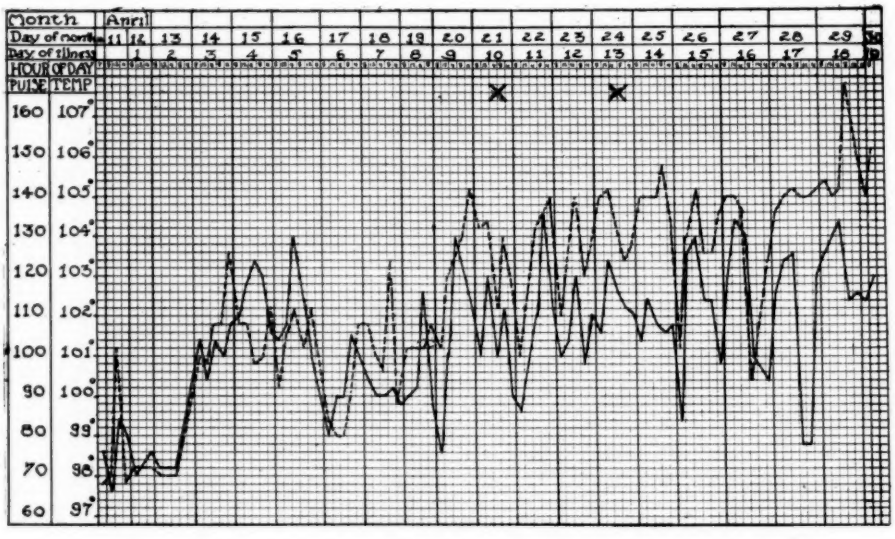

Fig. 6.

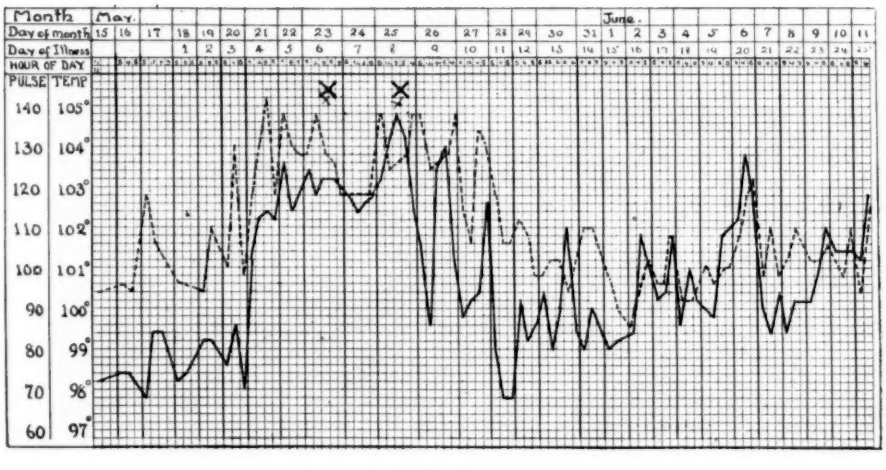

Fig. 7.

another 100 c.c. of serum was administered. The temperature dropped by lysis and the patient entirely recovered. (Fig. 8.)

3. M. K., para i, aged twenty-seven. This case had no prenatal care. She was admitted on April 1, 1922, and discharged on April 28. There were no rectal or vaginal examinations. No sutures were inserted.

The temperature rose to 102.4° on the fourth day and the following day to 104.6°. This patient had a chronic inflammation of the alveolar ridge of her mouth and

this had to be treated during her stay in the hospital. The blood culture was negative. The intrauterine culture was first reported as staphylococcus albus but later as sterile after 5 days. On the fourth day of the fever there was evidence of a double parametritis. Fifty c.c. of serum was administered after which the patient had a prolonged chill with cyanosis and shock. The temperature dropped to 97.8° with a pulse of 88. The following day the temperature rose to 104.4°. On the ninth day postpartum the leucocytes were 44,000 with 93 per cent polynuclear cells. Two days later the count dropped to 16,000 with 91 per cent polynuclear cells. On the twelfth day the temperature dropped to normal and on the twenty-first day without a rise in temperature there was an ischioretal abscess which was opened on the surgical ward and a dram or more of pus evacuated. The patient recovered. (Fig. 9.)

4. A. F. This patient was admitted to Bellevue Hospital on February 18, 1922. She was in the first stage of labor. There were no rectal or vaginal examinations, and the delivery was spontaneous.

On the third day the temperature rose to 104.2° and remained high until the ninth day when it reached normal. On the seventh day the blood culture was nega-

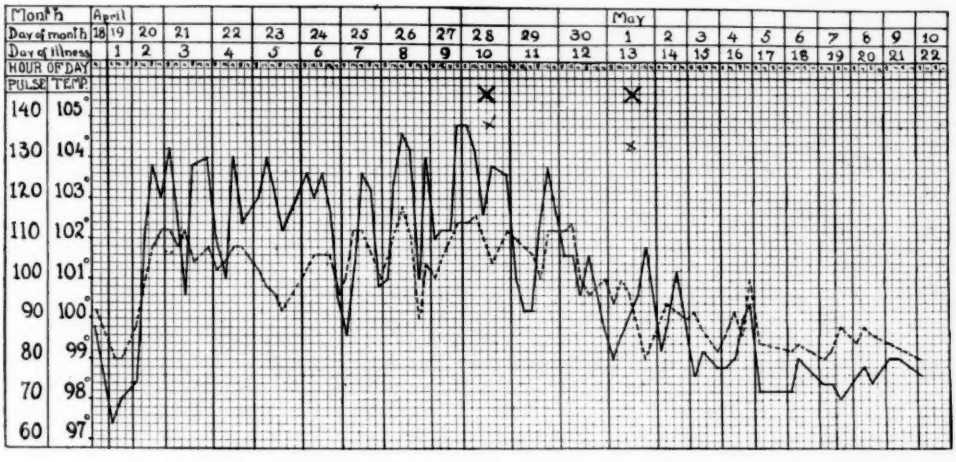

Fig. 8.

tive; one hundred c.c. of serum was given on this day and the dose was repeated on the following day. The temperature dropped almost at once and the patient gradually recovered and was discharged on March 9. (Fig. 10.)

5. M. U., para i. This patient was admitted to the Bellevue School for Midwives on March 6, 1922. She had had no prenatal care. She had a spontaneous delivery and one silkworm suture was placed in the perineum.

On the fourth day the temperature rose to 105° and remained as a continued fever until after the injection of the serum. On the fifth day of the fever 50 c.c. of serum was administered. On this day the leucocytes were 10,500 with 80 per cent polynuclear cells. The dose was repeated on the seventh day. The temperature gradually subsided to normal. The blood culture was sterile and the intrauterine culture was not taken. The patient developed a right parametritis. She was discharged on the 15th day. (Fig. 11.)

6. E. L. This patient was admitted to the Bellevue School for Midwives on February 17, 1922. She had a spontaneous delivery. A laceration of the perineum was repaired.

On the second day postpartum her temperature reached 104° and continued until

the twelfth day. On the seventh day the blood culture was taken and reported negative. On the seventh day the leucocytes were 14,600 with 88 per cent polynuclear cells. On this day the patient was given 50 c.c. of serum and immediately the temperature dropped to 100°. The following day it reached 104° and 100 c.c. of serum was given with a third dose on the ninth day. Temperature after reaching

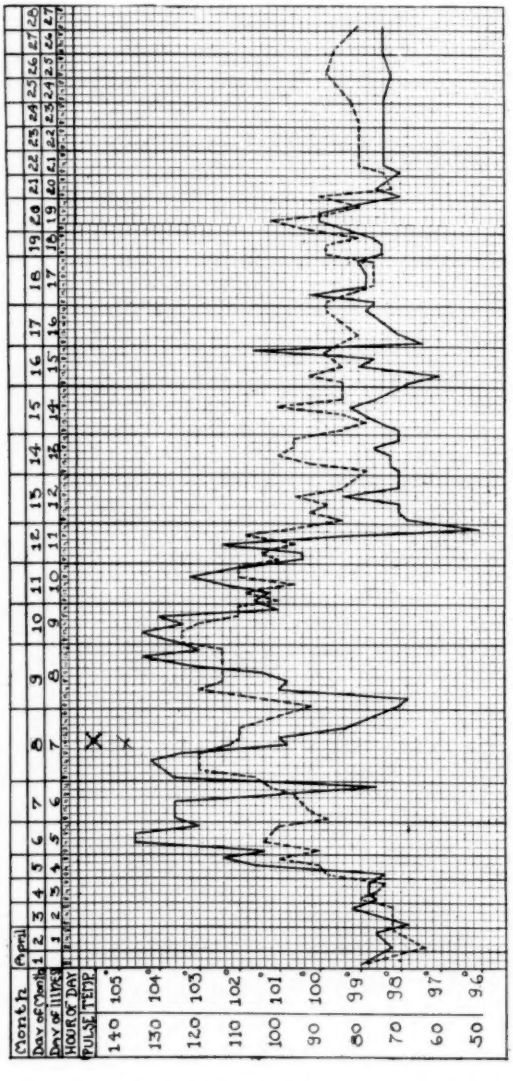

Fig. 9.

a high point of 105° dropped by lysis, reaching normal on the twelfth day. The patient entirely recovered. (Fig. 12.)

7. *A. M.*, para 1. Admitted to Bellevue Hospital on May 5, 1922, and died there May 17. This patient had had no prenatal care. The delivery was spontaneous and no rectal or vaginal examinations were made. The perineum was repaired with silkworm and catgut stitches. The Wassermann was 4-plus.

On the third day the the patient complained of a sore throat; the pharynx was congested and after a chill the temperature rose to 106°. The leucocytes were

23,000 with 86 per cent polynuclear cells. Without waiting for an intrauterine culture or a blood culture the patient was given 100 c.c. of serum on the fourth day. The temperature fell temporarily and the following day another dose of serum was given. The leucocytes were 13,200 with 84 per cent polynuclear cells. On the seventh day the third dose of 100 c.c. of serum was administered. The temperature fell by lysis and it was apparent that, while the patient was prostrated, she was improving. However, on the 11th day the pulse went to 150 while the temperature

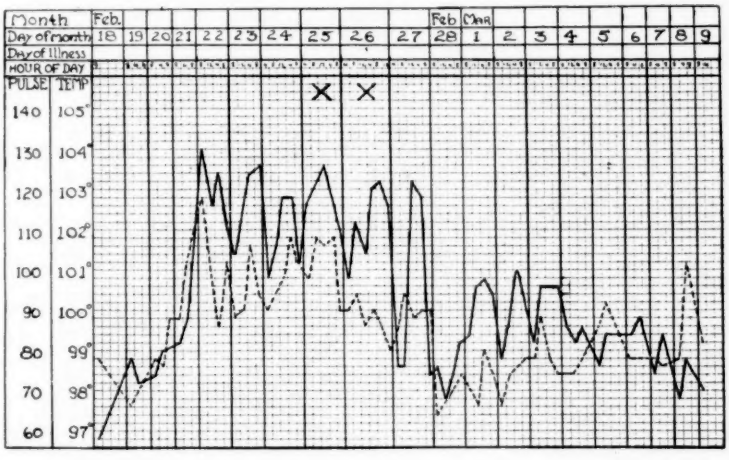

Fig. 10.

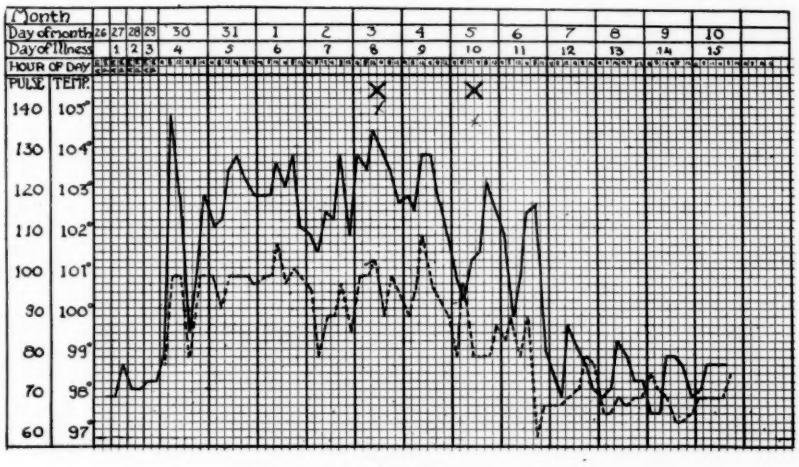

Fig. 11.

was going down. She died the following day. The temperature was 101° and the pulse 156 just before death. The day before she died the leucocytes were 23,000 with 86 per cent polynuclear cells. Possibly this patient had an embolism in her lung but no pulmonary signs were found. No autopsy was obtained. (Fig. 13.)

8. H. H., para i, aged twenty. A case from the prenatal clinic. She was admitted to Bellevue Hospital on May 9, 1922, and discharged on May 21. She returned to the Gynecological Ward on May 27 and died there June 4. The Wassermann was negative. She was admitted in labor and the delivery was spontaneous. There were

no rectal or vaginal examinations. The blood loss at the time of the delivery was somewhat above normal. There were no lacerations.

On the night of the fifth day the temperature rose, reaching 104° on the sixth day. The leucocytes were 15,800 with 82 per cent polynuclear cells and the following day they had reached 24,600 with 84 per cent polynuclear cells. One hundred

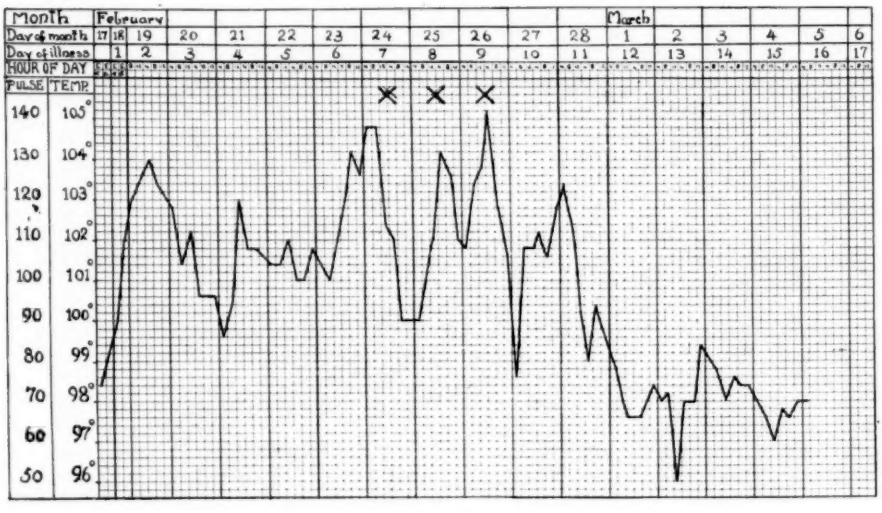

Fig. 12.

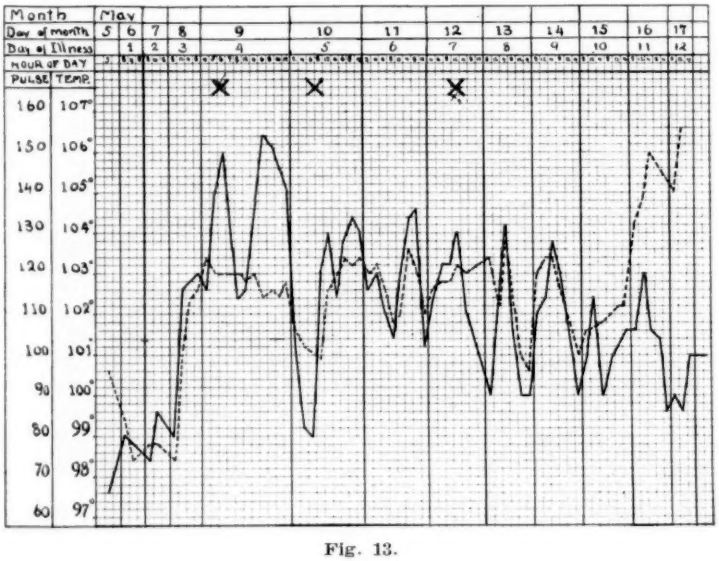

Fig. 13.

c.c. of serum was given on the 7th day, and the temperature dropped but rose again on the ninth day. Another dose of 100 c.c. of serum was given; the temperature dropped by lysis to normal. On the twelfth day the temperature reached normal and the patient had a marked parametritis on the right side. The uterus was fixed and rigid. The patient insisted upon going home notwithstanding our warning.

Six days later she returned to the Gynecological Ward with a temperature of

104°. She had an urticarial rash and considerable tenderness in the right parametrium. Serum sickness appeared on the eighth or ninth day after the second dose of serum. The leucocytes were 13,200 with 80 per cent polynuclear cells, and the red blood cells were 4,024,000. The temperature was high but intermittent, with a low point of 102° and a high of 105.4°. Two blood cultures were taken and both were negative. The patient died on the ninth day following her second admission. (Fig. 14.)

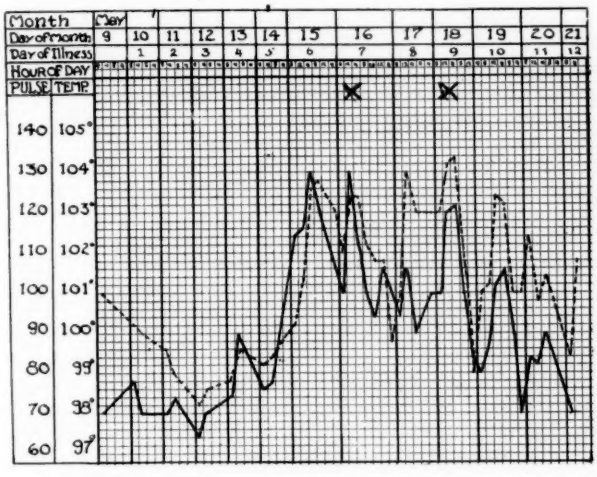

Fig. 14.

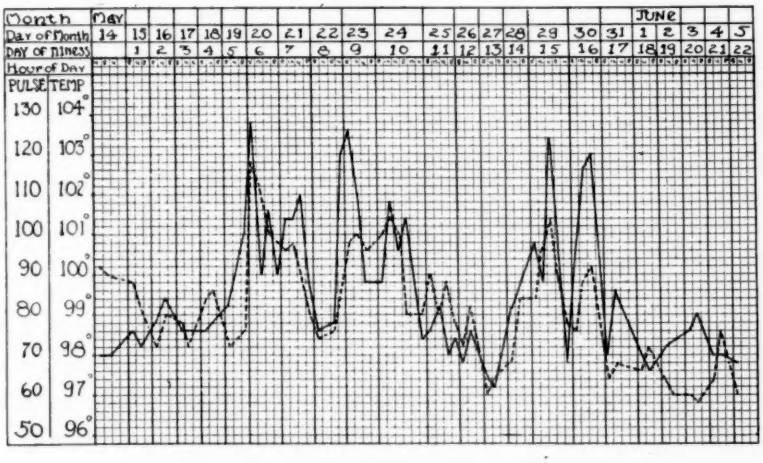

Fig. 15.

Group III.—Control Case.

1. B. D. This patient was admittted to Bellevue Hospital on March 14, 1922, and had a spontaneous delivery. No rectal or vaginal examinations were made.

On the fifth day the patient had a sore throat with considerable edema. The cultures showed streptococcus and pneumococcus. The temperature reached 103.8° on the morning of the sixth day; this condition was thought to be entirely due to the sore throat. The patient was segregated. The temperature reached normal on

the eighth day and rose on the tenth. There was a scant amount of lochia. The intrauterine culture was taken and found to contain streptococcus hemolyticus. The intradermal skin test was positive so that no serum was given. Two days later the temperature dropped to normal. There were two temporary rises on the fifteenth and sixteenth days. This undoubtedly was a case in which the infection was largely confined to the endometrium and shows that recovery may occur through the production of antibodies in the patient's own blood. (Fig. 15.)

DISCUSSION AND SUMMARY

The preparation of the serum must be efficient from a serologic standpoint. This means the proper injection of the animals with all the known procurable strains of hemolytic streptococci and the bleeding of them in order to obtain the immune serum at a time when the antigen is absent. The supply must be properly kept and it must not be too old. While these serums apparently can be reactivated as shown by Weaver and Tunecliff, especially by the addition of human serum, nevertheless there is a point at which reactivation ceases. The date as placed on the label should be an efficient guarantee that the serum is active or may be reactivated up to that day.

Desensitization must be carried out before the administration of the serum if there is the slightest doubt that the result of the dermal test is negative. With these precautions the serum may be considered as comparatively harmless, for although serum sickness appears in nearly three-fourths of the patients, this of itself, so far as we know, never produces fatalities. The usual symptoms are urticaria, joint swelling, and occasionally some edema of the throat may occur, either immediately after the injection or later on. It is true that one of our cases had a condition that simulated anaphylactic shock, but the method of administration in this case was by dilution so that the patient received in all 1,000 c.c. of the solution. Practical experience has shown us that this is not the best way of administering the dose. It is better to inject the serum very slowly without dilution. The dosage that we used might, in all cases, be termed moderate. We limited ourselves to the administration of 100 c.c. in 24 hours and when serum sickness appeared we gave no further injections. If this dose is repeated each day for three or four days, a sufficient amount may be received before the serum sickness appears. We believe that it is feasible to give more than one dose in 24 hours but we have not done so and it remains for some future observer to administer the larger doses. We believe that if the temperature rises in the postpartum period and remains above 103° for 48 hours, the dose of 100 c.c. should be given without waiting for the results of the cultures.

Parametritis occurred so regularly in our few cases that it seemed as though the serum had a tendency to localize the disease. The

serum treatment in the first days of the fever should be followed by the most careful treatment of the parametritis or the inflammation of the pelvic cellular tissues.

The mortality in the 6 cases that had positive intrauterine cultures of streptococcus hemolyticus was 16.6 per cent. In the second group, if we are permitted to discard the case that went home against advice on the first day that the temperature was down, but in the presence of a marked parametritis, and that later returned to the Gynecological Ward where she died, the mortality in the 7 cases remaining was 14.3 per cent. If we take the two groups together, 13 cases in all, the mortality was 15.3 per cent. If the death rate is uncorrected the mortality for the entire group is 21.4 per cent.

The only published statistical evidence that we have of the mortality in the recent cases in New York is the paper by Rosensohn[14] in which he analyzes the bacteremia occurring in the Lying-In Hospital from 1920 to 1922. In his group there were eight proved cases of streptococcus hemolyticus with a mortality of 62.5 per cent. There were three cases of nonhemolytic streptococcus and two with the streptococcus combined with B. coli. If the death rate from all these streptococcus cases including the two with mixed infections is taken, there was a total of 13, with a mortality of 61.5 per cent.

This discussion can hardly be closed without again mentioning Dr. Philip Williams' four cases of postabortal hemolytic streptococcemia in which the blood cultures were positive and which ended, after the administration of the serum, in a cure in each instance.

In conclusion, it may be stated that in 14 cases of acute puerperal fever, of which 6 had positive intrauterine cultures of hemolytic streptococcus, the administration of polyvalent antistreptococcus serum was followed in 11 cases by the subsidence of the temperature and gradual recovery, giving a death rate, uncorrected of 21.4 per cent and corrected of 15.3 per cent.

The administration of the polyvalent antistreptococcus serum, under the conditions outlined in this paper, appears to be comparatively harmless and of considerable value in the treatment of puerperal sepsis.

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119 East Seventy-fourth Street.

THE WASSERMANN TEST

III. A Statistical Study of Clinical Syphilis and Fetal Deaths in Women with Positive Wassermann Reactions

By David L. Belding, M.D., and Isabelle L. Hunter, B.S.,
Boston, Mass.

(From the Evans Memorial, Boston)

INTRODUCTION

IN a series of observations upon the Wassermann test in pregnancy at the Robinson Memorial of the Massachusetts Homeopathic Hospital, Boston, a comparative study of clinical syphilis and fetal deaths in 461 positive and 500 negative cases was made. The positive series was obtained from 5198 ward patients admitted during the years 1917 to 1920, of whom 9.2 per cent gave positive Wassermann tests. The negative series, selected for comparison, comprised the same proportion of racial and national groups, viz., American (two or more generations in the U. S. A.) 15.8 per cent, American (one generation in the U. S. A.) 40.3, Canadian 9.3, Jewish 9.1, Negro 7.2, Irish 7.4, English 2.6, Scotch 1.3, Armenian 1.3, Swedish 1.3, Greek 1.3, Teutonic 0.9, and miscellaneous 2.2. Five hundred cases are perhaps too small a number upon which to base definite conclusions but at least are sufficient to warrant a reasonable assumption of correctness.

The Wassermann tests were made with cholesterolized antigens according to the technic described by Belding and Adams.[1] All degrees of inhibition, as reported upon a 1 to 4-plus scale, were designated as positive. Separate consideration is given to strong or 4-plus positives. Unless accompanied by the prefix "Clinical" the term "Syphilis" refers to serum positive syphilis as determined by a positive Wassermann test. Since from 25 to 30 per cent of pregnant women giving positive Wassermann reactions with cholesterolized antigens are presumably nonsyphilitic, and a corresponding proportion of syphilitic women may have negative reactions, it is evident that our comparisons represent minimum rather than maximum differences. Owing to the fact that a relatively small number of positive cases received thorough prenatal antisyphilitic treatment and since many comparisons are based upon the history previous to diagnosis, the influence of treatment upon these statistics may be disregarded.

A. Clinical Syphilis in Pregnant Women

It is difficult to obtain a history of syphilis in pregnant women. Either they are ignorant of or are reluctant to disclose their condi-

tion. The symptoms usually associated with the disease are frequently absent or unnoticed by the patient, thus producing a clinical picture different from that of the typical syphilitic. Indeed, few cases present active lesions, the prevailing type being hidden or latent syphilis. The percentage of pregnant women with positive Wassermann tests who show clinical evidence of syphilis is variously estimated according to the interpretation of different authorities as to what constitutes a clinical diagnosis. The average of ten observers is 40 per cent, and practically all agree that the percentage is relatively low. Therefore, in the routine examination of a prenatal clinic it is possible in relatively few cases to obtain direct evidence of clinical syphilis.

A positive Wassermann reaction in pregnant women may not invariably denote syphilis, and, conversely, women with clinical syphilis sometimes give a negative test. If the commonly accepted estimate of 68 per cent positive in latent syphilis is correct, the reaction in pregnant women with syphilitic histories, largely of this type, should prove negative in less than 32 per cent. The average of 27 per cent negative in pregnant syphilitic women by four European observers confirms this statement, since a few cases of active syphilis would tend to reduce the number of negative Wassermann tests. Therefore, it would seem that serologic syphilis in pregnant women, as indicated by a positive Wassermann test, is by no means synonymous with clinical syphilis, each occurring independently of the other in an appreciable number of cases.

CLINICAL CLASSIFICATION

Our two series have been grouped from the standpoint of clinical syphilis into four classes: (A) *definite*, when there is no question of the clinical diagnosis; (B) *suspicious*, when there are several suggestive symptoms but the evidence is not conclusive; (C) *suggestive*, when a single symptom or sign of the disease is present; and (D) *no indication*, when no clinical evidence can be obtained.

The classification has been based upon the clinical findings as represented by physical examination, symptoms, history of infection, abortions, stillbirths, other children, husband and present child. This arbitrary method of presenting the clinical findings in four classes has several drawbacks: e.g., the necessity of taking into consideration the personality of the writer; the preponderance of symptoms in multiparae, and the corresponding paucity in primiparae; the impossibility of selecting only those abortions and stillbirths which are due to syphilis; the vaguely suspicious signs of syphilis which may occur in nonsyphilitics; and the frequency of confusing nonsyphilitic skin lesions in newly born children.

Two groupings have been made: (1) excluding present child, com-

prising the information which may be obtained in the prenatal clinic; (2) including present child, containing the additional information obtained from a clinical study of the offspring as long as the mother and child remained in the hospital, an average of thirteen days after delivery.

TABLE I

CLINICAL SYPHILIS

	EXCLUDING CHILD		INCLUDING CHILD	
	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
Number of cases	500	461	500	461
A. Definite	0.2%	5.9%	0.2%	9.8%
B. Suspicious	4.8%	11.7%	11.8%	19.9%
C. Suggestive	15.0%	21.5%	30.0%	25.2%
D. No indication	80.0%	60.9%	58.0%	45.1%

The presence of 0.2 per cent with definite clinical syphilis and 11.8 per cent suspicious in the negative series emphasizes the fact that a negative Wassermann, particularly in hidden and treated cases, does not rule out the diagnosis of syphilis. The greater part of the suspicious cases are nonsyphilitic owing to the frequency of suspicious signs in negative women, but a few may represent syphilities with negative Wassermann tests. Likewise, certain cases may be syphilitic and yet show neither a positive Wassermann nor clinical signs.

Classes A and B are alone worthy of consideration from a clinical or diagnostic standpoint, since a single sign or symptom of syphilis is so readily simulated by other conditions that Class C is approximately the same for both positive and negative series. Class A is unquestionably syphilitic, but Class B is a mixture of syphilitic and nonsyphilitic as indicated by the 11.8 per cent in the negative series which is due to the frequency of abortions, stillbirths, and other suspicious signs in nonsyphilitics. Naturally the nonsyphilitics included in the 461 positive Wassermann cases largely fall into the C and D classes, thus decreasing the actual percentage of the A and B classes.

Only 9.8 per cent of the positive cases gave definite evidence of syphilis and an additional 19.9 were suspicious, an increase of 9.6 and 8.1 per cent respectively over the negative series. Considering Classes A and B as presumably syphilitic and C and D as nonsyphilitic, 29.7 per cent of the positive Wassermann cases are clinically syphilitic as compared with 12.0 per cent of the negative cases. If the possibility of syphilis in the negative cases is disregarded, it would seem that the disease manifests itself clinically in 17.7 per cent of cases with positive Wassermann tests.

This clinical classification is subject to considerable modification and is markedly influenced by the following factors: (1) evidence of syphilis in the child of the present pregnancy; (2) the strength of

the Wassermann reaction; (3) the proportion of multiparae; (4) fetal deaths; and (5) race.

Present Child.—In about one-quarter of the cases, evidence of definite syphilis can be obtained only from the child of the present pregnancy. The additional evidence thus furnished gives a gain of 3.9 per cent for Class A and 8.2 for Class B. In the prenatal clinic where such data concerning the coming child is unobtainable, the difference between the negative and positive series is 5.7 per cent for Class A and 6.9 per cent for Class B, a total of 12.6, which probably represents the minimum figure.

Strength of Reaction.—Table II, which represents the findings in the prenatal clinic, shows the influence of the strength of the reaction upon the clinical classification. Contrasting the strong 4 plus with the weak 1 to 3 plus positives, differences of 8.3 and 7.8 per cent for Classes A and B are obtained, while the per cent of presumably clinical syphilitics is 25.6 for the strong positives vs. 9.5 for the weak. If the clinical findings in the present child are included, the difference is materially increased.

TABLE II

STRENGTH OF REACTION

CLINICAL SYPHILIS	NEGATIVE	POSITIVE			
		4 plus	1 to 3 plus	2 to 4 plus	All degrees
Number of cases	500	231	230	391	461
A. Definite	0.2%	10.0%	1.7%	6.4%	5.8%
B. Suspicious	4.8%	15.6%	7.8%	12.3%	11.7%
C. Suggestive	15.0%	21.2%	21.7%	21.2%	21.5%
D. No indication	80.0%	53.2%	68.8%	60.1%	61.0%

The strongly positive group includes a smaller per cent of nonsyphilitics since nonsyphilitic fixation more often occurs as a weak postive. Likewise, the weak positives represent old cases in which it is more difficult to obtain clinical evidence.

It is possible to obtain evidence of clinical syphilis in strong positives in at least 20.6 per cent in excess of the negative control series at the prenatal clinic, and in 27.8 per cent when the patient leaves the hospital. Evidently about 25 per cent of strongly positive Wassermann cases may give some evidence of clinical syphilis at the prenatal clinic.

In definite syphilis, Class A, the strong positives furnish 10 per cent, the weak 1.7, and the negative 0.2, indicating that the frankly clinical cases, unless treated, tend to give strong reactions.

The cases may be classified from the standpoint of reportable Wassermanns (2 to 4 plus), such as a laboratory would designate as positive, discarding the doubtful (1 plus) reactions. As such, there is an increase to 18.7 per cent in Classes A and B, with a corresponding

drop in the doubtful positives to 11.5 per cent. Including the present child, these figures total 32.0 and 17.2 per cent respectively. A similar change is also found in the definitely positive cases, which are 2.2 times more numerous in the reportable (2 to 4 plus) than in the doubtful (1 plus) positives. In the former, one case out of every sixteen, in the latter but one case out of thirty-four gave a definite history of syphilis. In view of the fact that 2.9 per cent of the 1 plus positives gave definite syphilitic findings and 8.6 per cent suspicious, as compared with 0.2 per cent and 4.8 per cent for the negative cases, it is evident that in pregnant women all grades of inhibition should be reported by the laboratory for clinical interpretation, otherwise in routine Wassermann tests a number of syphilities will be overlooked.

Primiparae vs. Multiparae.—In clinical comparisons, the primiparae and multiparae should be separated since in the latter the history of abortions, stillbirths, premature births and health of other children furnish considerable clinical evidence unobtainable in the former. In our series the proportion of multiparae runs 61.4 per cent for total positives, 62.3 for the strong positives, and 55.4 for the negatives, which, provided 500 cases are a sufficient number upon which to base conclusions, suggests that syphilis is more prevalent among the multiparae. This presumption seems reasonable in view of the greater possible exposure to the disease through longer married life.

TABLE III

PRIMIPARAE VS. MULTIPARAE

	PRIMIPARAE		MULTIPARAE	
Clinical Syphilis	Negative	Positive	Negative	Positive
A. Definite	0.5%	5.6%	0.0%	6.0%
B. Suspicious	0.9%	1.7%	7.9%	18.0%
C. Suggestive	1.3%	3.4%	26.0%	32.9%
D. No indication	97.3%	89.3%	66.1%	43.1%

In the negative series 1.4 per cent of the primiparae and 7.9 of the multiparae show a possible clinical syphilis. Correspondingly, the positive series gives 7.3 and 24.0 per cent. When the clinical findings in the child are included these figures increase to 4.5 and 18.1 per cent for the negative and 19.6 and 36.0 per cent for the positive. The increased percentage of the negative multiparae over the primiparae, approximately 5 to 1, suggests that many symptoms and signs in the multiparae simulate rather than indicate syphilis. Primiparae, therefore, afford a better comparison between the negative and positive series as regards the relative clinical findings of syphilis, but fail to give an adequate idea as to the total extent of clinical syphilis.

Class A shows a slight but uniform increase in favor of the multip-

arae for total positives, reportable positives, and strong positives, which is more marked when the additional evidence from the child is included. A similar increase is noticeable when the net gain over the negative control series is calculated. In both positive and negative series the multiparae show a great increase in Class B which is largely due to the number of nonsyphilitic fetal deaths and misleading facts concerning previous children. However, the net increase over the negative, 10.1 per cent, indicates that certain of these conditions in the multiparae are the result of syphilis.

Fetal Deaths.—The term fetal deaths includes both abortions and stillbirths. The causal relation between syphilis and fetal deaths is commonly accepted and this evidence, particularly when multiple, has been considered in our classification a sign of syphilis. The subject itself is sufficiently broad to demand separate treatment and, therefore, only that part which is concerned with the clinical classification will be considered here.

Of the negative multiparae, 33.2 per cent and of the positive 43.1 per cent gave a history of one or more fetal deaths, and correspondingly, 19.5 and 26.7 per cent of all conceptions resulted in fetal deaths. Therefore, if all fetal deaths are recorded as symptoms of syphilis, cases with nonsyphilitic fetal deaths will receive a false clinical classification. On the other hand, if all fetal deaths are eliminated the complete clinical picture will not be presented, since syphilis is directly or indirectly responsible for some 37 per cent of all fetal deaths in syphilitic women. By eliminating fetal deaths from the classification and considering only prenatal clinic evidence, the difference between the negative and positive series becomes more striking and the per cent of clinically suspicious syphilis, Class B, is greatly reduced. Only 0.6 per cent of the negative cases as compared with 9.1 and 14.7 per cent of the positive and strong positive fall into the probably syphilitic group.

TABLE IV

CLINICAL CLASSIFICATION EXCLUDING FETAL DEATHS

	NEGATIVE	POSITIVE	
		All Degrees	Strong (4 plus)
A. Definite	0.2%	5.2%	9.1%
B. Suspicious	0.4%	3.9%	5.6%
C. Suggestive	1.4%	11.0%	13.8%
D. No indication	98.0%	79.9%	71.5%

Race.—The reaction of different races to syphilis is interesting in view of the question of racial immunity or susceptibility to disease. Apparently a distinct biologic difference exists between the negro and the white races in their reaction to syphilis and less prominent demarcations occur between the various nationalities of the white race.

A comparison of the clinical findings in Americans of at least two generations, Negroes and Russian Jews, indicates considerable difference in the clinical classification.

TABLE V

INFLUENCE OF RACE

	NEGATIVE WASSERMANN			POSITIVE WASSERMANN		
Clinical Syphilis	American	Negro	Russian Jew	American	Negro	Russian Jew
Cases	200	142	200	69	27	43
A. Definite	0.5%	2.1%	0.0%	4.3%	14.9%	2.3%
B. Suspicious	5.0%	6.3%	3.5%	8.7%	25.9%	9.3%
C. Suggestive	12.0%	17.6%	13.5%	21.7%	29.6%	18.6%
D. No indication	82.5%	74.0%	83.0%	65.3%	29.6%	69.8%

The negative cases show a surprising uniformity with a slightly increased tendency toward clinical syphilis in the Negro, partly the result of a greater proportion of fetal deaths. The positive series indicates that clinical manifestations are especially marked in the negro and are least noticeable in the Russian Jew.

CLINICAL SYPHILIS

Clinical symptoms or a history of syphilis, especially when it is not primarily suspected, are difficult to obtain in the routine prenatal examination of the prospective mother owing to reticence or ignorance upon the part of the patient and to the absence of clinical manifestations. The infrequency of clinical signs of syphilis has been generally observed in both pregnant and nonpregnant women. Skinner[2] reports that women do not seek diagnosis or treatment at venereal clinics as early as men, owing to their lack of information concerning venereal disease and inability to recognize symptoms. Gellhorn[3] finds that the for concealment and that with the exception of fever and anemia the primary lesion is smaller, less indurated and tends to clear more rapidly, that the complexity of the female genitalia offers more chance secondaries are usually more fleeting. Gaucher[4] notes that the primary lesion cannot be demonstrated in 33 to 37 per cent of women while Polak[5] and Beck[6] conclude that the clinical history is of little use in the detection of syphilis in pregnant women. Therefore, it seems that clinical signs of syphilis in women, especially the primary lesion, may be absent or if present easily overlooked, in contrast to the more noticeable symptoms in men.

Sufficient evidence is not at hand to indicate whether syphilis in the pregnant woman differs from the nonpregnant since comparatively few cases of recent infection are found in routine obstetric examinations, the majority having contracted the disease previous to the present conception. Brown and Pearce[7] find that pregnant rabbits react differently from nonpregnant to experimental infection and that

this condition persists during the greater part of the lactation period. Evidently clinical syphilis is not only difficult to detect in women, but is particularly so during pregnancy.

Clinical syphilis in the pregnant woman may be determined by (1) symptoms, (2) history, (3) syphilis in the husband, (4) evidence in previous children and (5) congenital syphilis in the child. Only the first four sources are available at the prenatal examination, and of these there is little opportunity to obtain evidence of the disease in the husband or previous children. Consequently the prenatal examination is almost entirely limited to the physical examination and history of the patient.

The age, duration of married life, and a history of fetal deaths, although not in themselves diagnostic, furnish valuable confirmatory evidence and frequently the sum total may be sufficient to warrant a presumptive diagnosis. When arranged in five-year groups the percentage of the positives increased with age and duration of married life possibly owing to longer exposure to the common source of infection, the husband. The average age is 26.16 years for the negative and 26.52 for the positive cases. The average period of married life is about two months longer and the percentage of multiparae is greater for the positive than for the negative, 61.4 vs. 55.4.

The following tabulation of 60 definite syphilitic findings, in 44 cases shows the relatively small per cent, 0.95, of pregnant women who furnish direct clinical evidence of the disease. One other case not included here has been classed in our tables as definitely syphilitic because of the sum total of evidence.

TABLE VI

CLINICAL SYPHILIS	CASES
Symptoms in mother	5
History in mother	12
Husband	2
Previous children	1
Present child	11
Symptoms and previous children	1
History and husband	1
History and previous children	2
History and present child	4
Husband and present child	2
History, husband and present child	2
Symptoms, husband and present child	1
	44

In these 44 cases clinical syphilis was noted 60 times as follows: symptoms in mother, 7; history in mother, 21; husband, 8; previous children, 4; present child, 20. In 11 cases, 25 per cent, the diagnosis was made from congenital syphilis in the child with no definite

syphilitic sign except a positive Wassermann test in the mother. In the 33 cases where the diagnosis was made excluding the present child 9 had syphilitic children, although one-half had received antepartum treatment.

From the standpoint of the examining obstetrician with the prenatal clinic it would seem that the most fertile sources of information were (1) the history of the mother, 52.5 per cent; (2) the history of syphilis in the husband, 20 per cent; (3) clinical symptoms in the mother, 17.5 per cent; and (4) previous children, 10 per cent. If means were available for thorough investigation of each case, the husband and previous children would show a marked increase. Therefore, special attention should be paid in history taking to previous symptoms and treatment, and presumptive evidence in the form of fetal deaths should be carefully considered.

Symptoms.—Of 461 positive cases but 1.5 per cent gave definite clinical symptoms of syphilis in the mother and 1.3 gave suspicious, a meager total of 2.8 per cent. Since the patients were given a routine examination without special reference to syphilis, these figures are minimum but they emphasize the fact that insofar as the mother is concerned the type of syphilis is hidden. Twenty-two women showed symptoms directly or remotely referable to syphilis. Of these 7 were definitely and 6 suspiciously syphilitic, the remaining 9 presenting only headaches or gonorrhea. Unless accompanied by other reliable information headaches are of little importance and may be disregarded as a clinical sign owing to their frequent occurrence in other conditions. A greater number was found in the negative than in the positive series, 21 as compared with 12 cases, and in both instances where headaches were the only symptom there was no serious effect upon the offspring.

Unless infection occurred during the later months of pregnancy, it would be manifestly impossible in the prenatal clinic to detect the primary lesion. Active secondary lesions also are rarely found. Only four cases gave clearly defined secondary skin eruptions, while two others showed suspicious skin lesions. The negative cases gave one definite and one suspicious secondary. One case gave tertiary skin symptoms; two cases were definite neurosyphilities, and two others showed suspicious signs of neurosyphilis, in the form of neuritis and paralysis. The negative series contained one suspected case of aural syphilis.

History.—In 500 negative women one gave a definite history of syphilis, although four admitted gonorrhea. In 461 positive cases 21, 4.6 per cent, gave a definite and 11, 2.3 per cent, a suspicious history. In the 21 cases of definite syphilis, the average time between the discovery of the infection and the present confinement was five years,

the shortest one year, and the longest thirteen. Seven infections occurred within 2 years, 14 within six, 18 within nine and 21 within thirteen. The form in which syphilis was reported by the 21 patients was primary 14.3 per cent, secondary 52.4, neurosyphilis 9.5; and, through treatment alone 23.8. Eight cases had received treatment, of which one was in the primary, and two in the secondary stage, while five had no idea as to the stage of the disease. The examiner in the prenatal clinic, therefore, should pay special attention to a history of previous treatment and secondary manifestations.

Husband.—A definite history of syphilis in the husband was obtained in only 8 cases, 1.7 per cent, which is to be expected, owing to ignorance of the patient, concealment on the part of the husband, and the difficulty of obtaining an admission from either wife or husband. Our records of Wassermann tests on the husbands are few owing to the frequent refusal of the husband to submit to the test and the reluctance of the wife to tell her husband of her condition. However, negative Wassermann tests frequently occur in husbands of clinically syphilitic women or in fathers of syphilitic children.

Of the positive husbands 2 gave clinical symptoms and treatment, 2 a positive history and treatment, 1 clinical symptoms, positive Wassermann and treatment and 8 a positive Wassermann only. Three questionable luetic husbands were also noted but definite syphilis was not proved. Of the 8 positive husbands, 4 wives gave positive histories, 3 of whom had a single abortion and one 2 abortions and a stillbirth, while 4 showed no indication of the disease except 3 had abortions. Only 50 per cent showed definitely clinical evidence or history of infection, although all eight wives gave a strong (4 plus) Wassermann. Six children, 75 per cent, were definitely syphilitic and 2 were suspicious. Of the 8 husbands, 5 received more or less treatment, 3 were untreated. Of the 5 husbands treated, 4 children were syphilitic and one died of hemophilia neonatorum; while of the 3 untreated one child had snuffles, and two died of clinical syphilis. The three questionable cases gave two negative children and one syphilitic child.

In spite of the small number, these figures are significant. Either the infection of the wife occurred before the institution of treatment or treatment of the husband alone proved ineffective in preventing the transmission of the disease to mother and child. The high rate of syphilitic children, over 75 per cent, is especially striking, and warns the obstetrician where there is a history of syphilis in the husband, always to give antepartum treatment if there is the slightest suggestive clinical evidence or a positive Wassermann reaction of any degree in the prospective mother.

Previous Children.—In 674 conceptions in 283 multiparae with positive Wassermann tests, 180 fetal deaths occurred and 494 children

were born, of which 96 died within the first few years of life. Little information could be obtained relative to these dead children and suspicious findings were noted only in 14 cases with 23 dead children. Four children died of meningitis, one definitely syphilitic, one tuberculous and two unknown, but presumably syphilitic. Two of the four mothers were clinically syphilitic. In six cases which gave a history of early death in two to four children, only one mother was clinically syphilitic. In four cases where a child died during the first months of life, one mother was clinically syphilitic. Of the 398 living children only 23 gave a history of any trouble. Two had definite congenital syphilis, two had infected fingers and toes, two had infected mucous membranes, two had snuffles, two had snuffles and skin lesions, and thirteen had skin lesions in the form of rash, pustules and sores. As a rule information regarding previous children is so indefinite that it is of little value in the detecting of syphilis.

B. The Relation of Syphilis to Fetal Deaths

In this paper the term, "fetal death," includes both abortion and stillbirth, because in history taking it is frequently impossible to distinguish between the two. Arbitrarily, the delivery of a fetus which has not reached the stage of viability at the twenty-seventh to twenty-eighth week is termed an abortion, and one that has reached this stage but in which cardiac action has ceased during or before delivery is classed as a stillbirth. Statistics from maternity hospitals, where many patients are not under observations until the later months of pregnancy, are accurate in respect to the number of stillbirths but give no adequate idea of the number of abortions, which can be obtained only from the previous history of the patient.

Reproductive Power.—In our statistics which deal with pregnant women whose average age is about twenty-six years, the number of previous conceptions is 1.22 for the negative, 1.46 for the positive and 1.64 for the positive cases which had definite clinical syphilis. The difference, if any, lies in favor of the syphilitic series, irrespective of whether considered from the standpoint of the total cases, total multiparae or multiparae with a history of fetal deaths. Hata[8] states that 40 per cent of positive Wassermann women, married three years, do not become impregnated and concludes that syphilis is an important factor in the production of sterility. Our statistics, although not directly comparable since all the patients were pregnant, indicate that while syphilis may produce sterility it has no appreciable check upon the number of conceptions in women in whom fecundation is possible. Jeans[9] in a compilation of 881 positive and 350 negative cases from the literature finds no appreciable difference between the average number of conceptions in the syphilitic, 4.71 and the nonsyphilitic, 4.89.

Productive Power.—The productive power is measured by the ratio of the living children to the total conceptions. Although Table VII shows that the average number of conceptions is greater for the positive series, the average number of living children is lower. The difference in the percentage of living children between the negative, 69.7 and the positive, 59.1 is not as striking as the figures of 76.1 and 54.7 compiled by Jeans[9] for 1712 pregnancies in nonsyphilitic and for 1538 in syphilitic families. Nevertheless it definitely shows that serum-positive and more particularly clinical syphilis has an appreciable effect upon the productive power.

TABLE VII

SYPHILIS AND PRODUCTIVE POWER

	NEGATIVE	POSITIVE		CLINICAL SYPHILIS
		ALL DEGREES	STRONG (4 PLUS)	
Number of multiparae	277	283	144	30
Average conceptions	2.20	2.38	2.25	2.47
Average living children	1.53	1.41	1.19	0.73
Average fetal deaths	0.43	0.64	0.71	1.33
Total number of conceptions	610	674	325	74
Per cent living children	69.7	59.1	52.7	29.7
Total children born alive	491	494	223	34
Per cent dead children	13.4	19.4	23.3	35.3

Syphilis also increases the number of early deaths in children born alive. Our 13.4 per cent for the negative series agrees with the 15.0 for 1489 nonsyphilitic children compiled by Jeans,[9] but our 19.4 per cent for the positive is considerably lower than his 30.2 for 1366 children of syphilitic families, which is only exceeded by our 35.3 for clinically syphilitic mothers. These comparisons indicate that our statistics which deal with positive Wassermann tests in pregnant women are not comparable with clinical syphilis studies and at best represent minimum figures as to the effect of the disease.

INCIDENCE OF FETAL DEATHS

The incidence of fetal deaths may be obtained from the previous history of patients and from the records of maternity hospitals. If the mortality in the last months of pregnancy including parturition were as great as in the first six, statistics from these two sources would agree, but since it is estimated that a relatively small proportion of fetal deaths occur during the later period, results are not directly comparable. Furthermore, since syphilis as a causative factor is more in evidence in the last months of pregnancy, the statistics of maternity hospitals should furnish more reliable information as to the effect of this disease.

History of Fetal Deaths.—Table VIII indicates that 33.2 per cent of 277 negative multiparae, averaging 26.16 years of age and 2.2

TABLE VIII

HISTORY OF FETAL DEATHS

	CASES				CONCEPTIONS			
	NEGATIVE	POSITIVE	STRONG POSITIVE (4 PLUS)	CLINICAL SYPHILIS	NEGATIVE	POSITIVE	STRONG POSITIVE (4 PLUS)	CLINICAL SYPHILIS
Multiparae	277	283	144	30	610	674	325	74
Fetal Deaths								
Number	92	122	67	21	119	180	102	40
Per cent	33.2	43.1	46.5	70.0	19.5	26.7	31.4	54.1
Increase over negative		9.9	13.3	36.8		7.2	11.9	34.6

previous conceptions, have a history of one or more fetal deaths, whereas 1148 cases obtained from four sources in the literature give 30.7 per cent. Six hundred and ten conceptions in these women resulted in 119 fetal deaths, or 19.5 per cent. Similarly seventeen investigators of fetal deaths, irrespective of, or excluding, syphilis, average 18.2 per cent ranging from 7.7 to 33.3. In women with a history of fetal deaths 40.3 per cent of 280 conceptions resulted in fetal deaths while seven investigators of such families report 46.1 per cent.

Of 283 women with positive Wassermann reactions averaging 26.52 years of age and 2.38 previous conceptions, 43.1 per cent gave a history of fetal deaths as compared with 36.6 per cent of 231 syphilitic cases from four sources in the literature. The strongly positive and the clinically syphilitic cases showed a still further increase. In round numbers in every 100 multiparae 33 would give a history of fetal deaths if the Wassermann test were negative and 10 more if positive, or less than one-quarter (10 in 43 or 23 per hundred) would be the direct or indirect result of syphilis.

In 674 conceptions in women with positive Wassermann reactions fetal deaths resulted in 26.7 per cent, an increase of 7.2 per cent over the negative series. In round numbers our figures indicate that in every 100 conceptions 19 fetal deaths would occur if the Wassermann reaction were negative in the mother and 7 more if positive, or one-quarter (7 in 26 or 27 per hundred) of all fetal deaths in women with positive Wassermann reactions would be due to syphilis. In the same manner two-fifths (39 per hundred) of the strong 4 plus positives and two-thirds (64 per hundred) of the clinical positives would be due to syphilis.

In 8517 conceptions in syphilitic families where one or both parents were clinically syphilitic or where there was congenital syphilis in the children, reported from twenty-two sources, an average of 29.0 per cent of fetal deaths was found. If the figures of 18.2 and 29.0 per cent as compiled from the literature are approximately correct for nonsyphilitic and syphilitic families, by a similar calculation it would appear that over one-third (37.5 per hundred) of all fetal deaths in

the history of syphilitic families would be due to this disease. Since an unknown number of children were born previous to infection this figure represents the minimum effect of syphilis. The 37.5 per hundred, which corresponds with the 39 per hundred for our strong positives, adds further evidence that our total positive series contains an appreciable number of nonsyphilitics. This point is further demonstrated by the 64 per hundred of fetal deaths resulting from syphilis in women with a definite clinical history as well as a positive Wassermann reaction.

Hospital Fetal Deaths.—Table IX gives the percentage of fetal deaths and children dying within two weeks in three maternity hospitals. The statistics from the New England Hospital for Women and Children and the Massachusetts Homeopathic Hospital are taken from their respective reports for the years 1917 to 1920 inclusive and the Johns Hopkins Hospital figures from Williams.[10, 11]

TABLE IX

HOSPITAL FETAL DEATHS

HOSPITAL	LOCATION	TOTAL DELIVERIES	PER CENT FETAL DEATHS	PER CENT DEAD CHILDREN	PER CENT TOTAL
(1) New England Hospital for Women and Children	Boston	3187	3.30	3.26	6.56
(2) Massachusetts Homeopathic Hospital	Boston	6564	3.66	3.31	6.97
(1) and (2)	Boston	9751	3.54	3.29	6.83
(3) Johns Hopkins Hospital	Baltimore	14000	...	...	7.14
Total		23751	...	...	7.04

Since the three hospitals exercise the same skill in treating patients the difference is probably due to the class of patients and the number of emergency cases. At the Johns Hopkins Hospital where about one-half of the hospital population consists of negroes the rate is 5.14 for the white and 9.40 for the negro patients. Since negroes comprise less than three per cent of the patients at the two Boston Hospitals the statistics for whites at the three hospitals would be 6.56, 6.97 and 5.14 respectively. Unless exact information in regard to the social and economic status of the patients were obtained, comparisons between these hospitals would be futile. For practical purposes an average of 6.83 per cent may be accepted for the Boston Hospitals, of which slightly over one-half, 3.54, are fetal deaths. These figures include about 9 per cent of women with positive Wassermann reactions.

Statistics from 29 cities in the United States in a total of 487,985 registered deliveries in 1922 give an average of 4.35 stillbirths per 100 deliveries, which perhaps gives a better representation of the coun-

try than the more limited group in the two Boston Hospitals. Lack of uniformity in reporting and defining stillbirths in part accounts for the variation in the different parts of the country. Deliveries numbering 576,172 in Boston between 1891 and 1921 give an average of 3.57, a lower figure than the country as a whole. Eliminating the syphilitics, the Boston rate would probably fall to 3.22. In our selected series of 500 women with negative Wassermann reactions the rate was 3.6 and for 5960 negative women at Robinson Memorial 3.41.

Three investigators report 5.6 per cent of stillbirths in 1536 deliveries in syphilitic families, a figure which is probably too low since syphilis was not always demonstrable in the mother. Our positive series of 461 cases gave 6.1 per cent, which may be slightly high since it includes a few abortions. Our figures indicate that in every 1000 deliveries 36 stillbirths would occur in nonsyphilitics and 61 if the Wassermann test were positive, or two-fifths (25 out of 61 or 41 per cent) of all hospital fetal deaths in women with positive Wassermann reactions would be due to syphilis. Similarly in the strong 4 plus positives and the clinical syphilitics, which give 78 and 200 per thousand, one-half (54 per cent) and four-fifths (82 per cent) of all hospital fetal deaths will be due to syphilis.

Approaching the subject from the standpoint of fetal deaths and children dying in the hospital, our negative series of 500 cases gave 6.2 per cent and 5960 negative women at the hospital gave 6.74. Recalculating Williams'[11] figures, 1742 nonsyphilitic white women gave 5.0 per cent and 97 syphilitic 12.4, while our 461 positive women showed 9.1 per cent. Therefore, Williams finds 2.5 times as many fetal deaths and dead children in the syphilitic cases as in the nonsyphilitic, while our figures indicate only 1.47 times. Our strong positives and clinical positives which show 9.96 and 24.0 per cent respectively give 1.61 and 3.87 times.

SYPHILIS AS A CAUSE OF FETAL DEATHS

It is commonly considered that fetal deaths due to syphilis occur chiefly in the last half of pregnancy. If comparatively few syphilitic abortions occur in the first six months of pregnancy the proportion of syphilitic fetal deaths will be lower for the entire gestation period than for the last months, where the competing factors are largely the complications of labor, malformations in the child and toxic conditions in the mother. For this reason the percentage of fetal deaths due to syphilis should be lower when taken from the past history of patients than from hospital records, especially since in the former, infection may have taken place subsequent to an undetermined number of births. Our statistics indicate that 27 per cent of all fetal deaths in women with positive Wassermann reactions may be directly or indirectly at-

tributed to syphilis as compared with 41 per cent of hospital fetal deaths.

In statistics relating to the causes of fetal death considerable difference is found between the various groups. The lower the social scale the less complicated seems the mechanism of labor. Fetal and infant mortality varies with different races. Economic and social pressure may produce a higher proportion of induced abortions, both criminal and therapeutic. Lack of prenatal care and skilled attendants at delivery tend to increase the mortality. At all events statistics dealing with different social and racial groups are not suitable for comparative purposes.

Abortions.—If the statistics in the first part of this paper are approximately correct, fetal deaths result in 18.2 per cent of all conceptions irrespective of syphilis, and stillbirths occur in 3.4 per cent of births at maternity hospitals. Since practically all hospital cases are near the completion of pregnancy it appears that 14.7 per cent or four-fifths of all fetal deaths occur before the seventh month of pregnancy.

It is more difficult to determine accurately the relative causes of abortions than those of stillbirths owing to the number of induced abortions which most frequently occur between the beginning of the second and end of the fifth month, following the first realization of her condition by the pregnant woman. Owing to the natural reticence of women and physicians upon this subject it would seem that the average of 16.7 per cent of induced abortions in 623 cases reported by four investigators might be an underestimation. The causes of abortion are classed by Meyer[12] as accidental 8.7 per cent, induced 26.9, therapeutic 24.7, associated diseases 21.4 and other causes 18.3; and by Dougal and Bride[13] as accidental 18 per cent, induced 20, constitutional 25, syphilis 10 and undetermined 27.

The surprisingly small rôle played by syphilis is due to the difficulty of accurate diagnosis, the infrequency of the disease and the fact that its maximum activity is not evident until the later months of pregnancy. Hornung[14] in 30 cases of fetal death in syphilitic women found that none occurred before the fifth month, 13.3 per cent during the fifth and sixth, 50 during the seventh and eighth and 36.7 during the ninth and tenth, indicating that the infection of the child does not occur until the last half of pregnancy and that the greatest danger exists during the seventh and eighth months.

Hospital Fetal Deaths.—In compiling statistics relative to the cause of stillbirths and early deaths greater attention was given the detection of syphilis at the Johns Hopkins Hospital than at the two Boston hospitals cited above, with the result that in the latter certain syphilitic fetal deaths may have been classified under macerated fetus,

prematurity or various causes. For this reason the 28.8 per cent of syphilis in the former would appear more reliable than the 4.3 and 2.4 per cent in the latter, if it were not for the large proportion of negroes. Williams[11] in 302 cases of fetal and early death in a hospital found that 12.12 per cent in whites and 45.13 per cent in negroes were due to syphilis, which indicates that the incidence of syphilis as a cause of fetal deaths in the white races is considerably lower than 28.8 per cent.

TABLE X
CAUSES OF FETAL DEATHS IN HOSPITALS

	FETAL DEATHS		FETAL DEATHS AND DEAD CHILDREN				
	NEGATIVE	POSITIVE	NEW ENG. HOSPITAL	MASS. HOM. HOSPITAL	NEW ENG. HOSPITAL	MASS. HOM. HOSPITAL	J. HOP. HOSPITAL
Cases	500	461	3187	6564	3187	6564	14000
Fetal deaths	18	28	105	240	209	457	1007
Per cent	3.6	6.1	3.30	3.66	6.56	6.97	7.14
Causes by per cent							
Mechanism of labor	11.2	25.0	38.1	30.8	20.5	21.9	22.6
Condition of child	27.7	10.7	9.5	22.5	28.2	33.9	14.4
Condition of mother	...	3.6	10.5	8.8	9.6	5.7	8.0
Syphilis	...	7.1	3.8	3.8	4.3	2.4	28.8
Macerated fetus	38.9	17.9	28.6	11.6	14.4	6.1	...
Various and unknown	22.2	35.7	9.5	22.5	23.0	30.0	26.2

In comparing the three hospitals, the mechanism of labor, including suffocation, dystocea and placental abnormalities and the condition of the mother, are approximately the same. The relative number of deaths due to the condition of the child, which comprises prematurity, inanition, debility and deformity, is slightly higher in the Massachusetts hospitals, and doubtless in some instances is due to unrecognized syphilis. No macerated fetuses are listed at the Johns Hopkins Hospital, while appreciable numbers, some of which may have been syphilitic, are reported at the other two. The similarity in the causes of fetal death in the positive and negative series indicates that syphilis may act indirectly by lowering the general resistance, thus rendering the fetus susceptible to conditions otherwise insufficient to produce death. The stage of the disease in the mother is an important factor in determining the syphilitic involvement of the fetus, and our observations for the most part are based on old and latent syphilitics.

A macerated fetus not infrequently is considered almost conclusive evidence of syphilis. Three observers estimate that about 80 per cent of all macerated fetuses are syphilitic, while a fourth gives 25 per cent. The presence of nearly twice the number of macerated fetuses in the negative as in the positive series, raises some doubt as to the correctness of using the term, macerated, as synonymous with

syphilitic. Maceration depends not merely on the cause of death, but rather upon the length of time that the dead fetus remains in the mother. Syphilis often produces a macerated fetus, but other conditions may accomplish the same result, and the designation of syphilitic should not be applied without morphologic evidence of the disease or the presence of the Treponema.

Fetal Deaths Due to Syphilis.—The effect of syphilis may be shown by determining the number of syphilitics among women with a history of fetal deaths. Five investigators obtained an average of 19.5 per cent of positive Wassermann tests in 481 women with a history of fetal deaths. Four others in 354 cases of hospital fetal deaths found 21.2 per cent positive. Williams[10, 11] in 1007 cases of fetal death or children dying soon after birth, found 28.8 per cent syphilitic by autopsy, placental examination and Wassermann test.

Approximately 895 of the 2770 multiparae who were delivered at the Robinson Memorial Hospital had a history of fetal deaths. Of this number, 122 had a positive Wassermann test, indicating that only 13.3 per cent of all cases with a history of fetal deaths were syphilitic. Approximately 183 cases of hospital fetal death occurred in 5198 women who had received Wassermann tests, of which 28 or 15.3 per cent were positive. It would seem that the incidence of syphilis in cases with fetal deaths was only slightly above the average prevalence in the community, which in this instance was 9.2 per cent.

If from one-third to one-half of all fetal deaths in latent syphilitics can be attributed to syphilis and but 13.3 to 15.3 per cent of women with fetal deaths are syphilitic, the actual proportion of fetal deaths resulting from syphilis in the vicinity of Boston must be between 5 and 7 per cent, a surprisingly low figure in view of the high percentage cited by investigators whose observations have been limited to women with clinical syphilis.

FACTORS INFLUENCING THE EFFECT OF SYPHILIS UPON FETAL DEATHS

Multiple Fetal Deaths.—The effect of syphilis is more evident in cases with multiple fetal deaths. In the negative multiparae a history of a single fetal death was obtained in 25.3 per cent and of multiple in 7.9; and in the positive multiparae in 31.1 and 12.0 respectively. Thus in women with positive Wassermann reactions, one-fifth (6 out of 31 or 19.2 per hundred) of all single and one-third (4 out of 12 or 34.2 per hundred), of all multiple fetal death cases would result from syphilis. Similarly, the statistics of Goodman[15] show a proportion of 21.9 and 36.8 per hundred. The influence of syphilis is even more strikingly shown in cases with three or more fetal deaths where 82.1 per hundred are due to syphilis.

From the standpoint of total conceptions single fetal deaths occurred

in 11.5 per cent of the negative and 13.1 of the positive; and multiple in 8.0 and 13.6 respectively. Thus in women with positive Wassermann reactions, one-eighth (1.6 out of 13 or 12.3 per hundred) of the single and two-fifths (5.6 out of 13.6 or 41.2 per hundred) of the multiple fetal deaths would be due to syphilis; and in the strongly positive cases one-quarter (23.8 per hundred) and one-half (51.0 per hundred) respectively.

Previous Fetal Deaths.—The negative and positive cases with living children may be divided into two groups according to the presence or absence of previous fetal deaths. In the negative series, 92 cases with 161 conceptions, with a history of one or more fetal deaths, show 15.5 per cent of early deaths in the living children as compared with 12.4 for 185 cases with 449 conceptions with no history of fetal deaths. In 14 cases with multiple fetal deaths a further mortality of 20 per cent in 45 children was found. Evidently mothers with a tendency toward fetal deaths are apt to produce premature or weak children. In the positive series of 122 cases with 202 children with a history of fetal deaths, a mortality of 19.5 per cent was recorded; in 161 cases with 292 children with no fetal deaths, 19.3 per cent, and in 23 cases of multiple fetal deaths, 20.8 per cent in 53 children. It would seem that both syphilis and a tendency toward fetal deaths in non-syphilitic mothers are likely to produce weak children.

The influence of a history of fetal deaths upon the production of stillbirths or death within two weeks of the present child is shown in Table XI. Irrespective of syphilis, primiparae show a definite increase over the multiparae, and multiparae with a history of fetal deaths have many more fatalities than multiparae with no history. Syphilis further increased these differences.

TABLE XI

EFFECT OF PREVIOUS FETAL DEATHS UPON PRESENT CHILD

	NEGATIVE				POSITIVE			
	PRIMIPARAE	MULTIPARAE		TOTAL	PRIMIPARAE	MULTIPARAE		TOTAL
		WITHOUT FETAL DEATHS	WITH FETAL DEATHS			WITHOUT FETAL DEATHS	WITH FETAL DEATHS	
Number of deliveries	223	185	92	277	178	161	122	283
Per cent stillbirths	3.6	3.2	4.4	3.6	7.3	3.1	8.2	5.3
Children dying within two weeks	4.0	1.1	2.2	1.4	6.2	0.6	1.6	1.1
Stillbirths and dead children	7.6	4.3	6.6	5.0	13.5	3.7	9.8	6.4

Race.—The productive capacity of the Russian Jew, American of at least the second generation, and the Negro as measured by the surviving children show marked differences. In the negative Wassermann series the Negro produced the smallest percentage of living children, 57.1; the American, 68.4, and the Jew, 71.4; while in the positive

series these figures fell to 26.0, 56.2, and 69.5 respectively, demonstrating the serious effect of syphilis upon the productive capacity of the Negro. The prevalence of syphilis in this group is 7.7 per cent for the Russian Jew, 9.1 for the American, and 16.0 for the Negro. It is interesting to note that a corresponding difference in respect to fetal deaths exists between these races.

In 200 negative women of each race a history of fetal deaths was obtained in 29.5 per cent of the Jews, 29.0 of the American and 41.4 of the Negro. Similarly, the percentage of fetal deaths to total conceptions ran: Jew, 15.2; American, 21.4; and Negro, 25.8. These differences are not due to variation in the number of conceptions, which averaged for the Jew, 2.46, American, 2.06 and Negro, 2.14, nor can they be explained by greater frankness on the part of the Negro in giving a more detailed history of fetal deaths. Consequently they may be attributed to racial differences, lack of prenatal care, or susceptibility to accidental or induced abortions.

Serum-positive syphilis increases the percentage of cases with a history of fetal deaths, Jew, 44.4, American, 42.8, and Negro, 71.4 as well as that of fetal deaths to total conceptions, Jew, 23.2, American, 33.7 and Negro, 42.0. The small number of multiple fetal deaths among the Jews reduces the percentage in both negative and positive series. In every 100 fetal deaths in women with positive Wassermann reactions, the number due to syphilis is, Jew, 34.0, American, 36.5, and Negro, 40.0.

Fetal deaths are 1.33 times as common in the negro as in the white race in nonsyphilities, and 1.57 times in serum-positive syphilis. In every 100 conceptions in Negroes, computed on the incidence of 16.0 per cent prevalence of syphilis, 28 would result in fetal deaths, of which 7 would occur in women with positive Wassermann reactions, or 25 per cent. Correspondingly, in whites with an incidence of 8.9 per cent, 20 fetal deaths would occur, of which 2.4 or 12 per cent would be in women with positive Wassermann reactions. The ratio of whites to negroes for syphilitic fetal deaths, 1:2.08, is slightly above the 1:1.85 ratio for the incidence of serum-positive syphilis in the two races, and less than Williams'[11] 1:3.72 ratio for fetal deaths and children dying during the first two weeks of life.

Strength of Reaction.—The strongly positive cases invariably show a higher percentage of fetal deaths. A weak positive may indicate a treated case, syphilis of long duration, serologic idiosyncrasy on the part of the patient or a nonsyphilitic reaction, which is more frequently a weak than a strong positive. Therefore, the effect of syphilis as demonstrated in Table XII should be more pronounced in the strongly positive cases.

Clinical Syphilis.—Cases of definite clinical syphilis are 2.4 times more numerous among multiparae with a history of fetal deaths than

TABLE XII

STRENGTH OF THE REACTION

REACTION	CASES		CONCEPTIONS		CHILDREN	
	NUMBER	PER CENT WITH FETAL DEATHS	NUMBER	PER CENT FETAL DEATHS	NUMBER	PER CENT DEAD
4 plus positive	144	46.5	325	31.4	223	23.3
1 to 3 plus positive	139	39.6	349	22.4	271	16.2
Total positive	283	43.1	674	26.7	494	19.4
Negative	277	33.2	610	19.5	491	13.4

among those with no history. In every 100 fetal deaths in women with positive Wassermann reactions, 64 will be due to syphilis when there is definite clinical evidence and 16 if there is none. Even if one-half the nonclinical cases were not syphilitic, the number of fetal deaths due to syphilis could not exceed 32. Evidently clinical syphilis has a marked effect upon the birth rate, whereas latent does relatively little damage.

TABLE XIII

CLINICAL SYPHILIS AND FETAL DEATHS

	NEGATIVE	POSITIVE	
		NONCLINICAL	CLINICAL
Multiparae			
Number of fetal deaths	277	253	30
Per cent	33.2	40.0	70.0
Conceptions			
Number of fetal deaths	610	600	74
Per cent	19.5	23.3	54.1

SUMMARY

1. In the prenatal examination of 461 pregnant women who gave positive Wassermann tests with cholesterolized antigens, definite and suspicious signs of clinical syphilis were found in 17.6 per cent. When additional evidence was obtained from the child the per cent was increased to 29.7.

2. In 500 negative women of similar racial groupings 5.0 and 12.0 per cent were obtained in the same manner, indicating the impossibility of detecting all syphilitics by routine Wassermann tests and suggesting that only the differences between the negative and positive series, 12.6 and 17.7 per cent, should be considered the minimum figures for clinical syphilis.

3. Definite syphilis was found in 0.2 per cent of the negative and in 5.9 and 9.8 per cent of the positive women according to the exclusion or inclusion of evidence in the child. These low figures are due in part to nonsyphilitic fixation with cholesterolized antigens, and to the impossibility of making a thorough examination for syphilis in the rush of a prenatal clinic; but more especially are caused by the relatively small proportion of women infected with syphilis who show clinical evidence of the disease.

4. The strongly positive reactions give a higher per cent of clinical syphilis owing to the exclusion of nonsyphilitic positives and of old syphilitics in whom the Wassermann reaction is frequently weak and clinical evidence difficult to obtain. The presence of an appreciable amount of clinical syphilis in the doubtful (1 plus) cases indicates that all degrees of inhibition should be reported by the laboratory for clinical interpretation.

5. Both serologic and clinical syphilis are more prevalent among multiparae, possibly because of longer exposure and greater opportunity for obtaining clinical evidence. Owing to the numerous symptoms and signs in multiparae which simulate syphilis the primiparae give a better comparison between the negative and positive series but fail to give the full extent of clinical syphilis.

6. When fetal deaths are eliminated as symptoms of syphilis, the difference in clinical classification between the positive and the negative series is more striking, since only about one-third of fetal deaths in serum-positive syphilitics are due to syphilis.

7. Clinical manifestations of syphilis are most marked in the Negro and least apparent in the Jew.

8. In 25 per cent of the definitely syphilitic cases proof of clinical syphilis was obtained only from the child.

9. In prenatal examinations the sources of information have the following values in the detection of clinical syphilis: history 52.5 per cent; husband 20; clinical symptoms 17.5; and evidence in previous children 10.

10. Secondary symptoms, which comprise about one-half the total recorded, are the most readily recognized by both patient and physician.

11. The proportion of living children to total conceptions averages 69.7 per cent in women with negative Wassermann reactions, 59.1 in those with positive reactions and 29.7 in those with clinical syphilis. Syphilis materially lowers the productive power of the human race.

12. In 277 negative multiparae 33.2 per cent gave a history of fetal deaths and 19.5 per cent of all conceptions resulted in fetal deaths, whereas in 283 positive multiparae the corresponding figures were 43.1 and 26.7 per cent, and in 30 multiparae with clinical evidence of syphilis 70.0 and 54.1 per cent respectively.

13. Syphilis is responsible for at least one-quarter (27 per cent) of all previous fetal deaths in women with positive Wassermann reactions and for two-thirds (64 per cent) in clinical syphilitics. Similarly, from statistics compiled from the literature it appears that over one-third (37.5 per cent) of all fetal deaths in syphilitic women are due to syphilis.

14. Our statistics indicate that two-fifths (41 per cent) of all hospital fetal deaths in women with positive Wassermann reactions and four-fifths (82 per cent) in clinically syphilitic women are due to syphilis.

15. Including both stillbirths and children dying before leaving the hospital, 1.47 times as many fatalities occur in serum-positive syphilitic women as in nonsyphilitic, and 3.87 times as many in clinical syphilitic.

16. The designation of syphilitic should not be applied to a macerated fetus without morphologic evidence of the disease or the presence of the Treponema.

17. There are 13.3 per cent of cases with a history of fetal deaths, and 15.3 per cent of those with hospital fetal deaths give positive Wassermann tests. Since but one-third to one-half of all fetal deaths in women with positive Wassermann reactions are due to syphilis, the proportion of fetal deaths due to that disease must be between 5 and 7 per cent.

18. Syphilis is twice as frequently the cause of multiple as of single fetal deaths in women with positive Wassermann reactions.

19. Multiparae with a history of fetal deaths tend to produce more stillbirths and a greater early mortality in children born alive than those who had no previous fetal deaths. Syphilis further increases this difference.

20. Fetal deaths are 1.33 times more frequent in the negro than in the white races in nonsyphilitics and 1.57 times in serum-positive syphilitics. The incidence of syphilis among negroes with a history of fetal deaths is twice that of whites.

21. Women with strongly positive Wassermann reactions have a higher proportion of fetal deaths, 31.4, than the weakly positive, 22.4.

22. In women with clinical syphilis 64 per cent of fetal deaths are due to syphilis as compared to 16.3 in serum-positive cases without symptoms, which emphasizes the serious effect of clinical syphilis in the mother.

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80 EAST CONCORD STREET.

NATURAL IMMUNITY IN THE NEWBORN*

By Luther K. Musselman, M.D., New Haven, Conn.

(From the Department of Obstetrics and Gynecology, School of Medicine Yale University.)

INTRODUCTION

CLINICAL experience has shown that human individuals differ in their resistance to disease. Not only is this statement true for adults who show a pathologic lesion, but also for adults and infants who have no impairment of physiologic function. It is possible that the resistance of the individual may be modified at any time by environmental effects or that the factors which determine resistance may have been deficient at birth. As a result of the work of Ehrlich the natural immunity which is present in the newborn is regarded as a passive immunity; acquired either by placental interchange of preformed antibodies, by the transmission of antibodies through the mother's colostrum and milk, or through the intervention of both agencies. In view of the fact that the methods by which this immunity is conveyed have not been thoroughly evaluated, and since a study of them might prove of importance in interpreting clinical findings, investigations were made to ascertain the comparative value and the mechanism of these processes.

Accordingly it was pertinent to determine: (1) If the antibody content of the sera of normal mothers and of their infants is equal. (2) If unequal, is the difference due to an increased efficiency of the maternal serum associated with pregnancy, or is it due to a normally low potency of the serum of the newborn? (3) If the former condition is true, at what period in pregnancy does this increased effectiveness manifest itself? (4) If the latter is true, how and when does the serum of the newborn attain a value equivalent to that of the maternal serum? In other words, what is the process by which natural immunity is developed?

A review of the literature reveals very few studies which have been conducted upon man, and of these studies by far the greater number deal with the acquisition of artificially acquired immunity, rather than with that of natural immunity. However, since the development of natural immunity in man may involve a mechanism similar to that which functions in other species, and since the acquisi-

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tion of natural immunity may be through processes similar to those which operate in acquired immunity, a brief statement will be given of the available data bearing on these points. In order to facilitate this, the articles will be considered under the various types of antibodies which have been investigated, namely, the aggregating antibodies,—agglutinins, precipitins, opsonins—and the distintegrating antibodies, the lysins. In addition, investigations regarding other properties of sera, such as the complement, the ferments, the antiferments, and the purely chemical constituents, will be considered.

I. *Agglutinins.*—Among the various individuals examined by Grünbaum[43] to show the value of the agglutinative reaction for enteric fever, there were three cases of normal parturient women and their newborn. He observed that the mother's serum, even if diluted, possessed marked agglutinative properties for B. typhosus and the cholera vibrio, but that the serum of the newborn failed to show any action on B. typhosus and, in one instance only, showed a weak agglutinative action on the cholera vibrio. He concluded that the agglutinins of the blood were not inherited but were formed by the child in later life. Halban[44] found that the maternal serum possessed a greater agglutinating ability for rabbits' red blood cells and for bacteria than did the serum of the newborn. In a few cases, the serum of the newborn contained no trace of agglutinin. He was of the opinion that the chorionic epithelium of the placenta manifested a selective action in absorbing constituents from the maternal blood, and that the agglutinins should be considered as both innate and acquired, the former type being apparently independent of the mother. Schumacher[93] reported a series of forty-five cases in which he compared the agglutinating ability of the blood of normal (no history of typhoid infection) mothers and their newborn for B. typhosus. The undiluted sera of all of the mothers agglutinated the organisms and twenty-two of them continued to show this property in the dilution of 1 to 50. The undiluted sera of sixteen of the newborn failed to show any agglutinating ability, and in the dilution of 1 to 25 a reaction was observed with the serum of but one infant. In the cases where the serum of the newborn possessed this agglutinating property, it was always of a lower value than that of the corresponding maternal serum. Halban and Landsteiner[45] found that the agglutinating ability for rabbits' red blood cells was always greater in the maternal serum than in that of the newborn. In comparing the action of inactivated rabbits' serum on the red blood cells of mother and infant Schenk[88] found the maternal cells to be less susceptible to agglutination than those of the infant. According to v. Graff and v. Zubrzycki[42] and to v. Zubrzycki and Wolfsgruber,[109] hemagglutinins were almost uniformly absent from the serum of the newborn, although they were present in the maternal serum, v. Fellenberg and Döll[35] tested the agglutinins of mother and newborn for the staphylococcus, B. coli, B. typhosus, the paratyphoid bacillus and the cholera vibrio. In twenty-five cases the serum of the newborn contained more agglutinins than that of the mother, but in a few cases it showed little or no agglutinating power, while in thirty-seven cases the maternal serum possessed this property to a higher degree. The fact that the serum which showed a higher agglutination with one organism had a higher agglutinating power for the others suggests the nonspecificity of the reaction bodies involved. With heterohemagglutinins the maternal serum was always of a higher value than that of the newborn. Kraus and Löw[58] showed that the serum of newborn guinea pigs lacked agglutinating power for B. coli, although the serum of the mother possessed this property even in the dilution of 1 to 20. These results were confirmed by the

work of v. Eisler and Sohma.[32] Park[73] believed that the blood of young animals was comparatively free from bacterial agglutinins. Huddleson[50] was unable to find any relationship between the agglutinins of aborted fetuses and their dams, between pregnant cows and their fetuses, or between newborn calves and their dams, and concluded that agglutinins (also complement-fixing antibodies) were not transmitted from mother to fetus in utero. Reymann[80] tested the agglutinative action of the serum of goats and of their newborn kids for B. typhosus, B. coli, and for the red blood cells of the horse and rabbit. Although present in the maternal serum in the fourteen cases, agglutinins were demonstrable in the serum of but one of the kids.

Specific Agglutinins. (A) *B. typhosus.*—The examination of the body fluids of fetuses which were aborted by typhoid patients prior to the sixth month of pregnancy failed to reveal any intrauterine transmission of agglutinins. (Etienne,[33] Charrier and Apert,[19] Dogliotti.[24]) On the other hand, the serum of fetuses prematurely delivered because of a similar infection contained agglutinins. (Chambrelent and Saint-Phillippe.[81]) The serum of a premature infant of seven months' gestation, born seven weeks after the mother's recovery from typhoid fever, showed less agglutinating ability than the serum of the mother. (Mossé and Daunic.[70]) Another infant of similar age, born during the third week of typhoid fever in the mother, showed a high agglutinating ability (Scholtz[92]). This property of the serum probably depended upon an intrauterine infection of the fetus, and not upon an actual transmission of agglutinins from the mother. A nine months' infant, born during the course of typhoid infection of the mother, showed agglutinins to about 1/10 the value of the maternal serum (Schumacher[93]). Infants, born of mothers recently recovered from typhoid fever, showed agglutinins in their sera (Castaigne,[16] Courmont and Cade[22]). In cases where the mothers had typhoid fever from two to twenty-one years prior to parturition, the maternal serum and milk showed agglutinins, but the infant's serum did not (Kasel and Mann[53]). A mother, who developed typhoid fever while still nursing her child, showed agglutinins in the milk, but the infant's serum was negative (Achard and Bensaude[2]).

The offspring of rabbits, inoculated with typhoid bacilli six days prior to parturition, showed some agglutinins but less than the maternal sera (Widal and Sicard[107]). Guinea pigs, immunized during pregnancy, transmitted agglutinins to the offspring, the value of their sera being less than the maternal, but this property disappeared from the serum of the young within a few months (Remlinger[78]). Guinea pigs, which were immunized before the beginning of pregnancy, bore young which later developed a higher agglutinating ability than the mother (Jurewitsch[52]). Agglutinins seemed to be equal in fetal and maternal sera if immunization was carried out one to two months prior to parturition, but if performed later in gestation the value of the fetal serum was less than that of the maternal (Staübli[99]).

A goat, immunized late in pregnancy, gave birth to a kid which died without suckling. The maternal serum and milk showed a high content of agglutinins, but the serum of the kid failed to show any agglutinins whatever (Schumacher[93]).

(B) *B. abortus.*—The sera of newborn calves usually did not contain any agglutinins until the animals had suckled, although the sera and colostrum of the mothers were rich in these antibodies (Little and Orcutt[64]).

(C) *V. cholerae.*—Guinea pigs, immunized during pregnancy, transmitted the antibodies to their young (Achard,[1] Dieudonné[23]).

(D) *B. proteus.*—Guinea pigs, which were immunized during pregnancy, transmitted the antibodies to their offspring (Achard[1]).

Hemagglutinins.—Goats, which were immunized to the red blood cells of the sheep, failed to transmit any antibodies to the kids (Kraus[57]). Guinea pigs and rabbits, immunized to sheep's red blood cells, showed about the same concentration in the maternal and fetal sera (Bourquoin[11]). In man, the hemagglutinins have long been recognized as being of significance in the determination of blood groups. It is also known that in children the blood group is not usually established at birth, but makes its appearance after a period varying from a few months to a year. When it does appear, it may or may not be that of the mother. Obviously, in these instances where the maternal and filial groups differ, there has not been a transmission of hemagglutinins as such from the mother to the offspring and it is equally impossible to consider that the reaction bodies which characterize the group could have been conferred upon the child through the milk.

II. *Precipitins.*—Specific precipitins against human blood serum were found in the serum of the offspring of rabbits which were immunized during pregnancy (Merkel[66]). Dogs, which were immunized to horse and cow serum, gave birth to young that failed to show any precipitins in their sera at the end of four weeks, even though precipitins for these antigens were demonstrable in the milk of the mothers (Bertarelli[8]). In view of the assumed relationship between precipitin and the anaphylactic antibody, it is pertinent to mention that passive sensitization from mother to offspring has been noted by Rosenau and Anderson,[85] Friedemann,[38] Otto[72] and other investigators.

III. *Opsonins.*—Wright and Douglas[108] and, later, Much[71] found that the opsonic power of the sera of the newborn was equal to that of the maternal sera. Turton and Appleton[102] showed that the opsonic index of the serum of infants several days old, was lower than that of the maternal serum, and the work of Wells[106] demonstrated that the value of the opsonic index of infants decreased during the first few days of life, but later increased. He concluded that healthy breast fed infants possessed no "advantages" over healthy artificially fed infants, and that the antibacterial defense in children was not dependent upon the opsonic content of their sera. This opinion agrees with that of Amberg,[4] who believed that the increased opsonic power of the breast fed infant was dependent to some extent upon its state of nutrition. v. Eisler and Sohma[32] found that opsonin did not appear in the fetal guinea pig until the last third of pregnancy; that it reached the normal value at birth; and that in both rabbits and guinea pigs the opsonins of the newborn were the same as in the mother. Flamini[33] observed that the opsonins were lower in artificially fed infants and concluded that they varied with the weight of the child. Cathala and Leuquex[17] showed that the opsonic index of the blood of the newborn was slightly less than that of the adult, and that it diminished during the first days of life. Tunnicliff[100] found the opsonic index approximately equal in the mother and the newborn. The opsonic value of the infant's serum fell rather rapidly during the first few months of life, and it required nearly two years to regain the adult value. This investigator showed also that the phagocytic activity of the infant's leucocytes followed the same curves, but a longer period was required to reach the adult value. Sherman,[94] in his studies upon swine, found that opsonins increased with the age of the fetus; and that prior to birth the value of the fetus was slightly lower than that of the maternal animal.

IV. *Cytolysins.*—(A) Bacteriolysins.—Halban and Landsteiner[45] concluded from one experiment with the cholera vibrio that the bactericidal action of the maternal serum was greater than that of the newborn. Schenk[89] found that the bactericidal action varied in adults, but, in the three cases examined, the action of the maternal serum against B. typhosus, B. coli, the cholera vibrio and Staphylococcus albus was

always greater than that of the serum of the newborn. Variable results were obtained by v. Fellenberg and Döll.[35] The sera of their cases were tested especially against the cholera vibrio, although a few were tested against the paratyphoid bacillus. Sometimes the value of the maternal serum was higher than that of the newborn, while in other cases it was lower. They concluded that these antibodies were not transferred from mother to fetus.

(B) Hemolysins.—Resinelli[79] was the first to show that fetal serum contained less hemolysin than the maternal serum. Halban and Landsteiner[45] found in all instances that the hemolytic action of the maternal serum for rabbits' red blood cells was greater than that of the serum of the newborn, and observed that the maternal serum when inactivated possessed a greater lytic action for the red cells than the inactivated serum of the newborn. They concluded, therefore, that the newborn possessed all of the serum constituents, but in a lesser degree than the mother, the lessened serum properties being associated with a somewhat lowered resistance to infection. They were of the opinion that it was desirable to investigate at what time and in what way in extrauterine life the change of the serum (newborn) takes place. From his investigation of six cases, Schenk[88] concluded that the maternal serum contained about four times as much hemolysin for rabbits' red blood cells as did that of the newborn. Moreover, when the sera were inactivated the value of the maternal serum was always greater than that of the newborn. Polano[77] held that the blood of infants rarely contained hemolysin. v. Fellenberg and Döll[35] believed that natural hemolysin was not transmitted from mother to offspring, and that at birth the fetus, as concerns its normal antibody formation and cell chemistry, is a separate individual and not dependent upon its mother. Kopf[56] found that the serum of the newborn calf lacked hemolysin for guinea pigs' red blood cells, but that hemolysin was present on the fourth day of life and soon reached the titer of the maternal serum.

The transfer of an artificially acquired antibody from immunized mothers to their offspring has likewise been investigated. Goats, which were immunized to the red blood cells of cattle (Kreidl and Mandl[59]) and to the red blood cells of sheep (Kraus,[57] Famulener[34]) usually failed to transmit hemolysin to their offspring, but, when the antibody was found, the titer of the kids' sera was very low. As the value of the kids' sera rose after suckling, and as the colostrum possessed a very high hemolytic value, Famulener[34] concluded that the sera of the newborn acquired their increased hemolytic action directly from the ingested antibodies. Bertino[9] noted that rabbits immunized before conception failed to transmit the lysins to their offspring, while Howell and Eby[49] found less hemolysin in the serum of the newborn than in that of the immunized maternal rabbits. Bourquoin[11], on the other hand, in rabbits and guinea pigs immunized to sheep's red blood cells, obtained approximately the same values in maternal and fetal blood. Bertarelli[8] failed to obtain any transmission of immune hemolysin in sheep.

Antitoxins.—Experiments have been carried out on the transfer of antitoxins from mother to offspring. Not only have the antitoxins from the bacterial toxins been investigated (Ehrlich and Hübener,[27] Römer,[84] Anderson,[5]) but those for the plant toxins (Ehrlich[26]) and for the snake venoms (Fraser[37]) have been studied. There is a uniform agreement that antitoxic immunity is transmitted in utero. However, the rapid disappearance of these antitoxins from the blood of the newborn suggests that the process is a purely passive heterogenetic immunization, and indicates that it results from the placental transfer of the antitoxin rather than from a transfer of the toxin. But it must be added that the injection of pregnant guinea pigs with antitoxic horse serum brings about an antitoxic immunity and at the same time a horse serum sensitization.

Antiferments.—Hamban and Landsteiner[45] demonstrated that the maternal serum possessed a stronger antiferment action than the serum of the newborn. Likewise, Becker[7] noted that the titer of the serum of the newborn was lower than that of the maternal serum, although the value of the latter was raised during pregnancy. Gammeltoft[39] corroborated this finding for man, but did not obtain similar results with cows and rabbits. On the other hand, Reymann[81] noted that the sera of newborn kids were of a higher titer than the maternal sera, the value of which was usually increased during pregnancy.

Antilysins.—Antilysins for the bacteriolysins have been measured for such organisms as B. megaterium, the staphylococcus and V. cholerae. For the antivibrolysin the antilytic value of the serum of the mother and of the offspring was equal (Schenk,[88] Reymann[82]). Similarly, Schenk[88] reported equal values for the maternal and fetal sera for the antistaphylolysin. For the antimegatheriolysin (Reymann[82]) and the antistaphylolysin (Polano,[77] Reymann[82]), the value of the maternal serum was higher than the serum of the offspring.

Complement.—In view of the fact that complement is necessary for the activation of many of the antibodies which may play a rôle in the processes of immunity, numerous investigators have associated individual immunity with the amount of complement in the blood. Buchner[13, 14, 15] termed the protective substance of the blood "alexin," and Bordet[10] showed that "alexin" was not increased by the process of immunization. As the latter investigator obtained similar results in working either with bacteria or red blood cells, Ehrlich and Morgenroth[28, 29, 30, 31] attempted to explain the phenomena of bacteriolysis by a study of hemolysis. They concluded that hemolysis was due to the combined action of a heat sensitive and a heat stable substance. The former corresponds to "alexin," is not specific and is not increased by the process of immunization; the latter, "amboceptor," is specific and is increased by immunization. The heat stable substance was bound to the red blood cells and thus rendered them susceptible to the heat sensitive substance which Ehrlich termed complement.

Gozony[41] showed that the serum of the rabbit at birth lacked hemolytic complement, but by the twelfth day the complementing value was the same as the maternal. Adair[3] comparing the sera of mother and newborn commonly found that the content of hemolytic complement in the sera of the newborn was less than, or equal to, the maternal value, while in a few cases the value of the sera of the newborn exceeded that of the mother. An anticomplementary substance was found in a few of the sera of the newborn which did not show any complement. From observation of the infants' weight curve, temperature chart, development of jaundice, etc., he concluded that there was no apparent relation between complement and nutrition, but that there appeared to be a relationship between hemolytic complement and immunity, as indicated by febrile reactions in the newborn.

Complement fixing antibodies.—Rosencrantz[86] noted in a series of 100 cases that 31 newborn children showed tuberculous antibodies in their sera, but no attempt was made to associate these findings with the incidence of tuberculosis among the mothers. Cooke[20] found that the serum of infants, at birth, possessed complement fixing substances, and the findings in these sera agreed very closely with the results obtained with the sera of the mothers taken several months after parturition. The substances disappeared from the infants' blood stream by the third month. Hence, he considered that the antibodies were transmitted from mother to child through the placenta, rather than through the milk. Likewise Ribadeau-Dumas, Cuel and Prieur[83] demonstrated that children born of tuberculous parents had in their sera antibodies which disappeared within one to three months.

SUMMARY OF REVIEW

With one exception the results of the investigations of the content of normal agglutinins show that the maternal serum is always of a higher value than the serum of the newborn. In some cases, the newborn failed to show any appreciable amount of this antibody. On the other hand v. Fellenberg and Döll[35] found in 25 out of 62 cases that the value of the serum of the newborn was greater than the maternal. However, they, as well as Grünbaum,[43] Halban[44] and others, were of the opinion that the newborn was independent of the mother for its antibodies.

There is considerable variation in the results of the cases which were examined for specific agglutinins. Fetuses which were aborted by women ill with typhoid fever, failed to reveal any trace of agglutinins. Infants born during a typhoid infection of the mother showed agglutinins, but always of a lesser value, while infants born of women who had typhoid fever prior to gestation, failed to show any agglutinins. Guinea pigs and rabbits which were immunized against B. typhosus or the cholera vibrio during pregnancy, gave birth to young which possessed some agglutinins, but less than the mothers. No transfer of this antibody was obtained in the goat. Infants born of tuberculous women, usually showed some antibody content in their sera. Hemagglutinins were not transmitted by sheep to the offspring, but guinea pigs and rabbits showed about the same concentration in the maternal and fetal bloods.

The content of bacteriolysins was found to be higher in the maternal serum than in that of the newborn, with the exception of a few of the cases examined by v. Fellenberg and Döll.[35] Human maternal serum was found by all to possess a higher content of hemolysins than the serum of the newborn, which in some instances failed to show any appreciable amount. Immunized goats usually failed to transmit any hemolysin to their offspring. Rabbits and guinea pigs which were immunized during pregnancy, showed about the same value in the maternal and fetal blood. However, Howell and Eby[49] found a lower content of hemolysin in the serum of the offspring of rabbits as compared with the maternal serum. In the serum of the offspring of sheep or rabbits which were immunized before conception, no hemolysins were found.

The results of the investigations of the content of opsonins in the serum of mother and newborn are in agreement. The value of the serum of the newborn was about equal to that of the maternal serum; it fell within the first few days of life, but subsequently rose. With reference to precipitins, the human maternal serum was always of a higher value than that of the newborn. The offspring of immunized

dogs failed to show any precipitins in their sera, but precipitins were found in the sera of the offspring of immunized rabbits.

The antiferment action was found to be greater in the human maternal serum than in that of the newborn, but in such animals as the goat, cow and rabbit, different results were obtained. In goats the content of antilysins was found to vary with the type of antilysin measured.

It is impossible to correlate all of the findings reported by the various investigators. It is conceivable that one species of animal transmits antibodies, both natural and acquired, to the offspring, while another species does not. It may be that placental transmission of antibodies is dependent upon the type of placentation; but it is difficult to understand why different results were obtained in the same species. Obviously, such factors as the species of animal, the nature of the antibody investigated, the method, and in cases of immunization both the nature of the antigen as well as the time and degree of immunization, must play important rôles. Clinical experience has shown that if a mother has developed an infection such as typhoid fever or small-pox in the latter months of pregnancy, the child is more likely to show evidence of such an infection than if the disease had occurred during the early months of gestation. In view of these diverse opinions, it was important to repeat some of the experiments and to perform others, to determine if possible how the newborn obtains its antibodies.

EXPERIMENTAL WORK

The antibody content* of the serum of normal mothers and their newborn may be determined by estimating the content of agglutinins, hemolysins, opsonins, precipitins, or bactericidins. It has been shown that the agglutinin titer of an individual's serum is not proportional to his resistance to a given disease; that hemolysins vary in the same species; and that, as our methods of determination are not very accurate, opsonins vary considerably. For these reasons, it was decided that a determination of the bactericidal action of the serum, that is, the ability of the serum to bring about the death of pathogenic organisms, would be the best single criterion from which to judge resistance or immunity (natural).

The experimental work in this paper is divided into the following sections:

1. The determination of the bactericidal action of the blood sera of mother and newborn.

2. Similar determinations upon the sera of men, of nonpregnant women, and of women in various months of pregnancy.

3. Complement titrations upon the sera of mother and newborn.

*The term "antibody" is used in the sense of "reacting body," and may or may not be synonymous with "immune body."

I. The Determination of the Bactericidal Action of the Blood Sera of Mother and Newborn

A. Technic. (a) *Method of securing specimens.*—The blood of the newborn was obtained from the umbilical cord following delivery, but before the placenta had separated. The cord was dried with a sterile gauze sponge, painted with tincture of iodine, and the specimen was obtained by puncture of one of the cord vessels with a sterile needle, or the cord was cut through this sterilized area and the blood collected in a sterile glass tube. The maternal blood was obtained from an arm vein at approximately the same time and under aseptic conditions. The majority

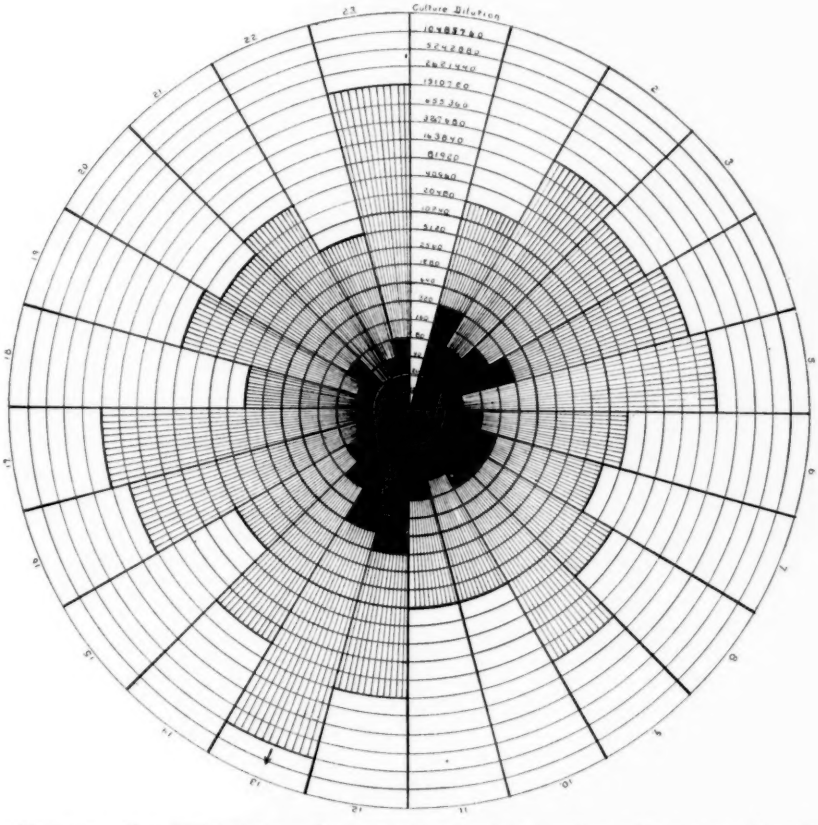

Chart 1.—The comparative values of the bactericidal action of the sera of mother and newborn. The solid area indicates the bactericidal value of the maternal sera while the radii indicate that of the sera of the newborn. Example, in Case 1 the maternal serum permanently inhibited bacterial growth in the culture dilution of 1:640 while the serum of the newborn did not show this property until the culture was diluted 1:40,960.

of the specimens, which were kept in the ice box until utilized, were tested within a few hours after they were obtained, and none of the specimens was more than 14 hours old. The native, unheated serum was separated by centrifugalization, and was not diluted for the tests.

(b) *Preparation and standardization of culture dilutions.*—An 18 hour broth culture of a strain of B. typhosus was diluted 1/10, 1/20, 1/40, 1/80 etc. for the tests. Agar plates each containing one-tenth of a cubic centimeter of

TABLE I

CASE	GRAVIDA	DURATION OF LABOR	DELIVERY	ANESTHETIC	CHILD		WEIGHT ON DISCHARGE	REMARKS
					SEX	BIRTHWEIGHT		
1*	8	12 hours	Spontaneous	None	M	2765 gm.	2835 gm.	Antiluetic treatment for 5 years, Wassermann reaction still positive. (+ with alcoholic antigen.)
2	1	5	Low forceps	Nitrous oxide and ether	F	2740	2870	
3†	7	30½	Spontaneous	Chloroform	M	2600	2775	In 4th month of pregnancy a radical operation for unilateral mammary cancer performed. Local recurrence with palpable nodules in liver. Infant had mixed feeding.
4†	1	15	Breech extraction	Nitrous oxide	M	2440	4420	Preeclamptic toxemia; labor induced. Femoral thrombophlebitis in puerperium. Infant had mixed feeding.
5	1	16	Version and extraction	Nitrous oxide and ether	F	3345	3210	Unilateral pyelitis in 7th month of pregnancy. Infant had mixed feeding.
6	1	8½	Low forceps	Nitrous oxide and ether	F	3355	3190	Infant had mixed feeding.
7	1	8	Spontaneous	lt. chloroform	M	3330	3155	Infant had mixed feeding.
8	2	13	Spontaneous	" "	F	3570	3915	
9	1	11½	Spontaneous	" "	F	2545	2735	
10	4	6	Spontaneous	" "	F	3350	3525	

TABLE I—CONT'D.

CASE	GRAVIDA	DURATION OF LABOR	DELIVERY	ANESTHETIC	CHILD SEX	CHILD BIRTHWEIGHT	WEIGHT ON DISCHARGE	REMARKS
11*	11	38	Version and extraction	Nitrous oxide and ether	F	3420 gm.	....	Fetus was dead when patient was admitted. Thrombophlebitis of broad ligament vessels in puerperium.
12	2	5	Spontaneous	Nitrous oxide and lt. chloroform	F	3495	3670 gm.	
13†	1	23	Low forceps	None	M	2820	3045	Eclampsia with 6 intrapartum convulsions. Labor induced. Infant had mixed feeding.
14	2	9½	Spontaneous	lt. chloroform	M	2770	2810	
15	2	30	Spontaneous	" "	M	2715	2910	
16	4	4½	Spontaneous	" "	M	3120	3320	
17	5	7	Spontaneous	" "	F	3060	3340	Mother and infant had ++++ Wassermann reactions.
18	1	16½	Spontaneous	" "	M	3520	3820	
19	2	14	Low forceps	Nitrous oxide and ether	M	3635	3660	
20	3	2	Spontaneous	lt. chloroform	M	3230	3335	
21	4	10½	Spontaneous	" "	F	3520	4105	
22	2	16	Version and extraction	Nitrous oxide and ether	M	3365	....	Infant died in 5 hours from intracranial hemorrhage.
23	2	5	Spontaneous	None	M	2985	3260	

*The microscopic examination of sections of these placentas and umbilical cords revealed a polymorphonuclear infiltration of the subamniotic connective tissue and of the vessels of the cord, which is called placental bacteremia and omphalitis respectively.
†Cases 3, 4 and 13 were in the hospital 16, 70 and 20 days respectively, due to maternal complications.

culture were poured in each test, in order to know the number of organisms per c.c. in the 18 hour culture. The plates were kept in the incubator at 37° C. and the colonies counted at the end of 48 hours. This time interval was found to give more reliable counts as artifacts were avoided. The 18 hour broth cultures showed counts varying between 2000 and 2800 colonies per 1 c.c. in culture dilution of 1:13,107,200.

(c) *Preparation of apparatus.*—Capillary looped pipettes were made following the technic of Wright. A piece of glass tubing about 24 cm. in length was heated in the middle, drawn out to a capillary, broken, and then a loop made in the upper portion of the capillary. The large ends were plugged with cotton and the pipettes sterilized by dry heat at 170° C. for two hours.

(d) *Method of performing the test.*—A small mark was made about 3 cm. from the capillary end of the sterile pipette by a wax pencil and the end flamed. Dextrose Andrade broth* was aspirated above the loop. Serum was drawn up to the mark, and a similar amount of culture, the two being separated by a small column of air. These were forced out in a sterile Petri dish, thoroughly mixed by repeated

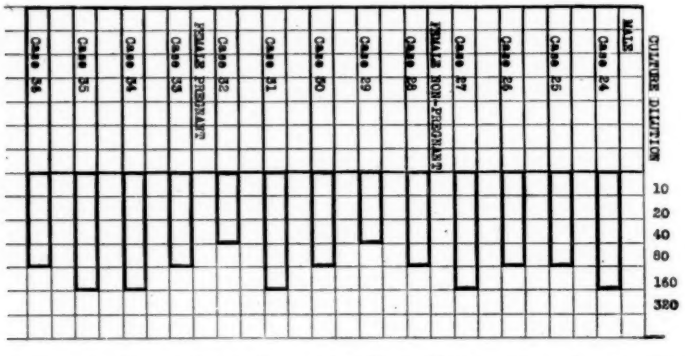

Chart 2.—The values of the bactericidal action of the sera of men, nonpregnant women and women in various months of pregnancy.

aspiration and expulsion and drawn back into the capillary portion of the pipette, the end of which was sealed in the flame. The pipettes were immersed in a water-bath at 37° C. for three hours. The ends of the pipettes were then broken, the culture and serum mixture was drawn up above the loop, where it mixed with the dextrose Andrade broth, and the end of the pipettes were again sealed. The pipettes were now incubated at 37° C. and the readings made at the end of 36 hours. The end point, namely, the culture dilution in which the serum completely inhibited growth of the typhoid bacillus, was easily determined by examination of the pipettes, since viable typhoid bacilli ferment the dextrose, yielding an acid which reacts with the Andrade indicator. Control pipettes were prepared to test the sterility of the serum and to demonstrate the presence of viable typhoid bacilli in the higher culture dilutions.

B. Abstract of cases (Table I).—These determinations were carried out on the sera of patients admitted to the Woman's Clinic of the New Haven Hospital. In all instances, they were normal, healthy mothers, without evidence of any acute infectious process that might modify determinations of this kind. Unless stated to the contrary in the following abstracts, it is to be assumed that the patients gave no history of a typhoid infection; that the past history was irrelevant; that

*This is a meat infusion broth to which 1 per cent of Andrade indicator has been added.

the puerperium was uneventful; that the Wassermann reactions were negative; that the microscopic examination of the placental and cord sections was negative for syphilis, placental bacteremia and omphalitis; that the infants were breast fed and that they showed no abnormality during their stay in the hospital.

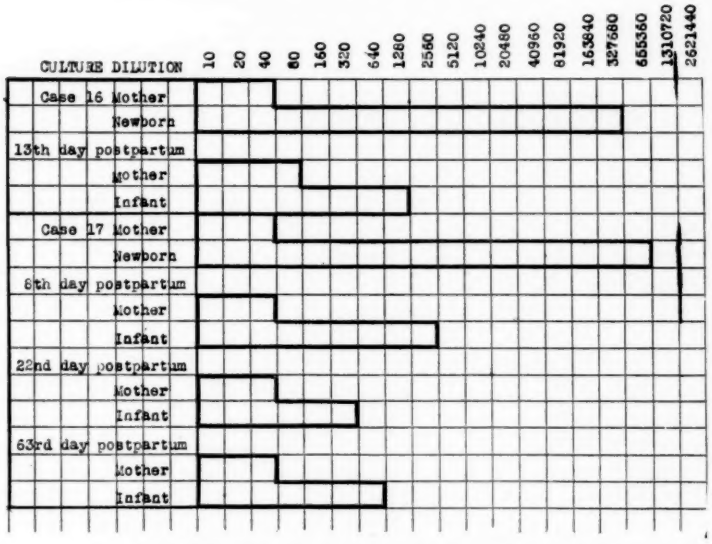

Chart 3.—The bactericidal values of the sera of mother and child at birth and later in the puerperium. In Case 16 one determination on the thirteenth day of the puerperium was made; while in Case 17 determinations were made on the eighth, twenty-second, and sixty-third days. In the former, the bacterial counts by the plate method were 2100 and 2400 colonies respectively per 1 c.c. in the culture dilution of 1:13107200; while in the latter the bacterial counts by the same method and in the same culture dilution were 2120, 2200, 2850, and 2500 colonies respectively.

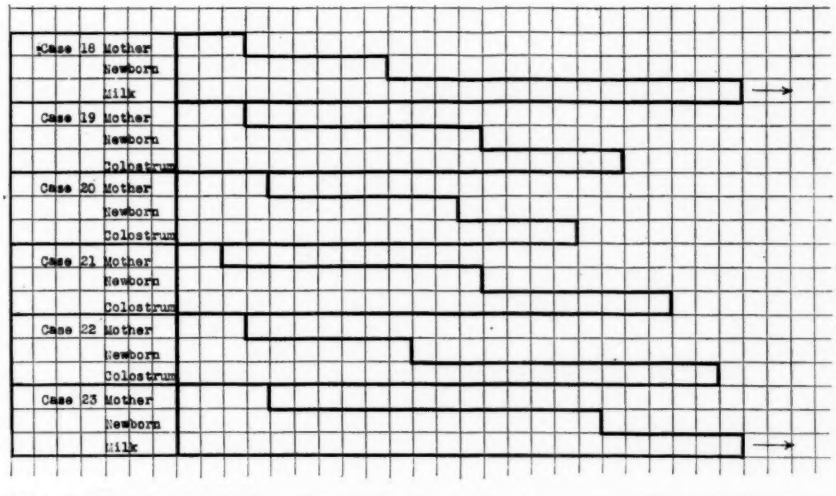

Chart 4.—The bactericidal action of the sera of mother and child at delivery contrasted with that of colostrum and milk obtained during the puerperium.

C. Summary of results.—In the 23 cases included in Chart 1, it is seen that the maternal serum is invariably more effective in its bactericidal or bacteriostatic action than is the serum of the newborn. However, this difference in values varies.

In general, the sera of the newborn were effective in culture dilutions from six to fourteen times those in which the maternal sera inhibited bacterial growth. This could not be correlated with any known factor such as the sex or the birth weight of the infant, the weight curve during the first two weeks of life, the nationality or multiparity of the mother, the duration or character of the labor or the administration of an anesthetic.

II. The Determination of the Bactericidal Action of the Sera of Men, of Nonpregnant Women, and of Women in Various Months of Pregnancy.

A. Technic.—The specimens were secured and the tests were performed following the method already outlined.

B. Notes on Cases.—(Table II).

C. Summary of results.—(Chart 2).

The bactericidal value of the sera was found to vary somewhat in adults. However, it can be seen that these values are approximately equal in men and in women; and that the sera of pregnant women have about the same bactericidal value as those of nonpregnant women. Hence, pregnancy in itself is not responsible for an increase in the bactericidal value of the serum.

TABLE II

CASE	SEX	REMARKS
24	male	Typhoid fever in 1906. Typhoid vaccine innoculation in 1918. Under treatment for an infection of operative area following an amputation of lower right leg.
25	"	Under treatment for cerebrospinal syphilis.
26	"	Cystitis and hematuria of undetermined origin.
27	"	Alveolar abscess of third lower molar, associated with osteomyelitis of left mandible.
28	female nonpregnant	Recovering from mild case of bronchopneumonia.
29	" " "	Myomatous uterus and cervical polyp.
30	" " "	Menorrhagia of undetermined origin.
31	" " "	Repair of old complete laceration of the perineum performed.
32	" " "	Postoperative hernia. Under treatment for syphilis, but Wassermann reaction continued ++++.
33	female pregnant	Acute bronchitis in 7th month of pregnancy.
34	" "	7 months pregnant.
35	" "	2 months pregnant.
36	" "	6 months pregnant.

III. The Comparative Values of the Complementing Activity of the Sera of Mothers and Newborn

The marked difference in the bactericidal values of the sera of mother and of newborn indicates that there is a fundamental difference in the content of serum constituents. Biologic bactericidal action is usually assumed to be dependent upon the union of an antigen with its

specific antibody with the activation of the complex by complement. The difference between the values of mother and newborn may be referable to an inadequate complementing property or to a deficiency

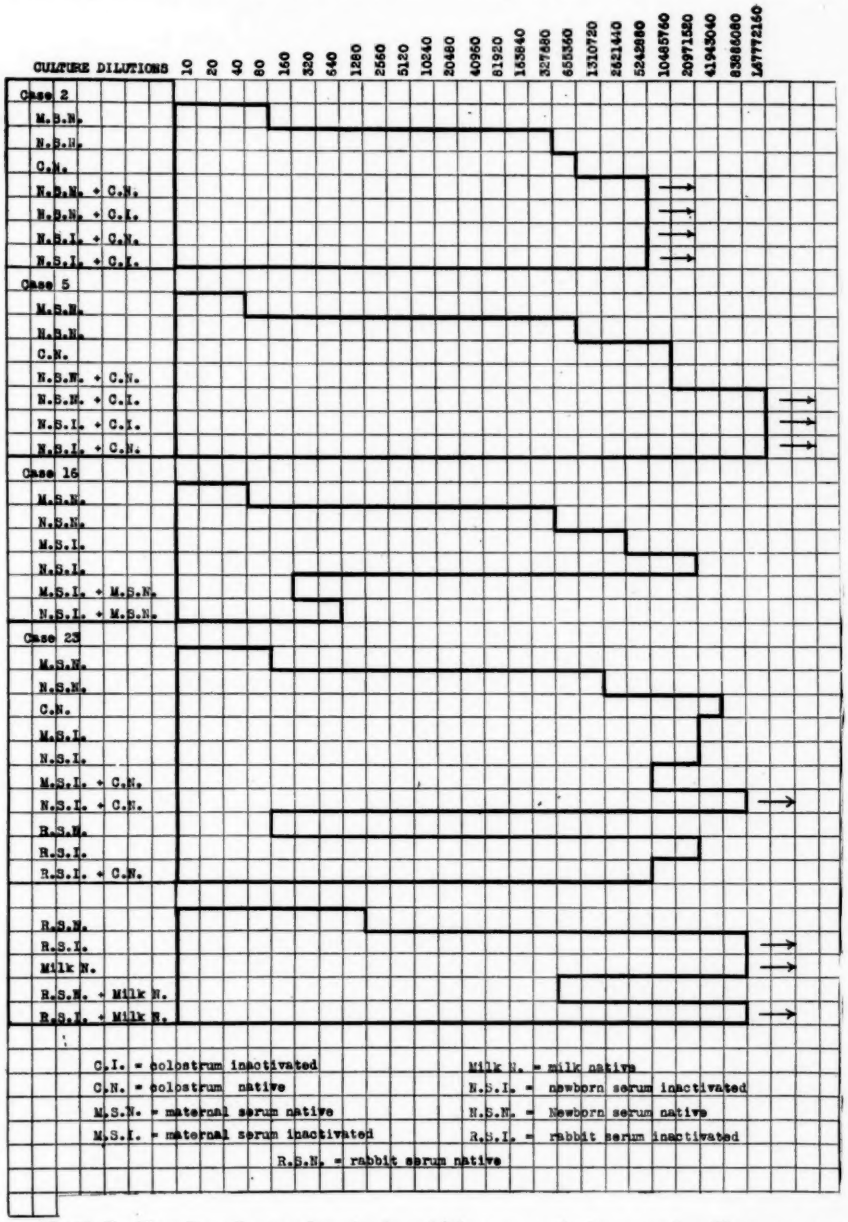

Chart 5.—Results of experiments in which sera, colostrum and milk were combined both native and inactivated, to determine if the bactericidal action depends upon a thermolabile or a thermostabile antibody.

in antibody. It appears that complement titrations upon the sera might explain the nature of the deficiency.

A. Technic.

(a) *Serum.*—Some of the sera which were obtained for the bactericidal tests were used.

(b) *Amboceptor.*—The anti-sheep hemolytic system was used.

(c) *Red blood cells.*—The sheep's cells were washed and suspended in saline to a concentration of 2.5 per cent.

(d) *Method of titration.*—The native serum was diluted 1 in 5 or 1 in 10 with physiologic salt solution. Variable amounts of this dilution were tested against one unit of amboceptor and 0.5 c.c. of the cell suspension. The total volume in the tubes was made up to 2.5 c.c. with saline. They were then incubated at 37.5° C. for 20 minutes.

B. Experimental Findings.—

CASE 2

TUBE	AMBOC. 1 UNIT	SERUM 1:5	CELLS 2.5%	SALINE	RESULT* HEMOLYSIS MOTHER	CHILD
1	0.4 c.c.	0.1 c.c.	0.5 c.c.	1.5 c.c.	+++	0
2	0.4	0.2	0.5	1.4	++++	++
3	0.4	0.3	0.5	1.3	++++	++++
4	0.4	0.4	0.5	1.2	++++	++++
5	0.4	0.6	0.5	1.0	++++	++++
6	0.4	0.8	0.5	0.8	++++	++++
7	0.4	1.0	0.5	0.6	++++	++++
8	..	1.0	0.5	1.0	++++	0

CASE 9

TUBE	AMBOC. 1 UNIT	SERUM 1:5	CELLS 2.5%	SALINE	HEMOLYSIS MOTHER	CHILD
1	0.4 c.c.	0.1 c.c.	0.5 c.c.	1.5 c.c.	0	0
2	0.4	0.2	0.5	1.4	++	0
3	0.4	0.3	0.5	1.3	++++	+
4	0.4	0.4	0.5	1.2	++++	+++
5	0.4	0.6	0.5	1.0	++++	++++
6	0.4	0.8	0.5	0.8	++++	++++
7	0.4	1.0	0.5	0.6	++++	++++
8	..	1.0	0.5	1.0	0	0

*++++ indicates complete hemolysis (100%)
+++ indicates marked hemolysis (75%)
++ indicates partial hemolysis (50%)
+ indicates slight hemolysis (25%)
0 indicates no hemolysis

CASE 12

TUBE	AMBOC. 1 UNIT	SERUM 1:5	CELLS 2.5%	SALINE	HEMOLYSIS MOTHER	CHILD
1	0.4 c.c.	0.1 c.c.	0.5 c.c.	1.5 c.c.	0	0
2	0.4	0.2	0.5	1.4	0	0
3	0.4	0.3	0.5	1.3	+++	0
4	0.4	0.4	0.5	1.2	++++	+++
5	0.4	0.5	0.5	1.1	++++	++++
6	0.4	0.6	0.5	1.0	++++	++++
7	0.4	0.8	0.5	0.8	++++	++++
8	0.4	1.0	0.5	0.6	++++	++++
9	..	1.0	0.5	1.0	++++	0

CASE 16

TUBE	AMBOC. 1 UNIT	SERUM 1:5	CELLS 2.5%	SALINE	HEMOLYSIS MOTHER	HEMOLYSIS CHILD
1	0.4 c.c.	0.1 c.c.	0.5 c.c.	1.5 c.c.	++++	0
2	0.4	0.2	0.5	1.4	++++	++
3	0.4	0.3	0.5	1.3	++++	+++
4	0.4	0.4	0.5	1.2	++++	++++
5	0.4	0.5	0.5	1.1	++++	++++
6	0.4	0.6	0.5	1.0	++++	++++
7	0.4	0.8	0.5	0.8	++++	++++
8	0.4	1.0	0.5	0.6	++++	++++
9	..	1.0	0.5	1.0	0	0

CASE 17

TUBE	AMBOC. 1 UNIT	SERUM 1:5	CELLS 2.5%	SALINE	HEMOLYSIS MOTHER	HEMOLYSIS CHILD
1	0.4 c.c.	0.1 c.c.	0.5 c.c.	1.5 c.c.	+++	0
2	0.4	0.2	0.5	1.4	++++	++
3	0.4	0.3	0.5	1.3	++++	++++
4	0.4	0.4	0.5	1.2	++++	++++
5	0.4	0.5	0.5	1.1	++++	++++
6	0.4	0.7	0.5	0.9	++++	++++
7	..	0.7	0.5	1.3	++++	0

CASE 19

TUBE	AMBOC. 1 UNIT	SERUM 1:5	CELLS 2.5%	SALINE	HEMOLYSIS MOTHER	HEMOLYSIS CHILD
1	0.4 c.c.	0.1 c.c.	0.5 c.c.	1.5 c.c.	0	0
2	0.4	0.2	0.5	1.4	0	0
3	0.4	0.3	0.5	1.3	0	0
4	0.4	0.4	0.5	1.2	0	0
5	0.4	0.6	0.5	1.0	0	0
6	0.4	0.8	0.5	0.8	++++	0
7	..	0.8	0.5	1.2	0	0

As the titration of the sera of the mother and of the newborn in this case showed such a low content of complement in the maternal serum and an absence of complement in the serum of the newborn, it seemed pertinent to determine whether this finding was due to a deficiency of complement or to the presence of anticomplementary substances. The same hemolytic system was used, but a sublytic quantity of guinea pig complement was added to each tube.

CASE 19 (CONTINUED)

TUBE	GUINEA PIG COMPLEMENT 1 unit = 1.5 c.c.	AMBOC. 1 unit	SERUM 1:5	CELLS 2.5%	SALINE	HEMOLYSIS MOTHER	HEMOLYSIS CHILD
1	1.0 c.c.	0.4 c.c.	0.1 c.c.	0.5 c.c.	0.5 c.c.	++++	++++
2	1.0	0.4	0.2	0.5	0.4	++++	++++
3	1.0	0.4	0.3	0.5	0.3	++++	++++
4	1.0	0.4	0.4	0.5	0.2	++++	++
5	1.0	0.4	0.5	0.5	0.1	++++	++
6	1.0	0.4	..	0.5	0.6	++++	++++

The results of this titration show that the decreased hemolytic action of the maternal serum is due to a deficiency in complement, while the lack of hemolysis by the serum of the newborn depends upon the presence of anticomplementary substances.

C. Summary of results.—In the six cases examined, the complement titrations conform to the findings in the bactericidal tests, namely, the value of the maternal

serum is greater than that of the newborn. Although both of these serum principles stand in the same relationship between mother and offspring, there is no parallelism between them. In Case 19, the bactericidal value of the maternal serum was approximately equal to that of the other cases, but there was a deficiency of complement, as compared with the other titrations.

It appears, then, that the sera of mother and child differ in their content of complement, but the difference in the bactericidal values of the two sera cannot be explained by this factor alone, as the serum of one infant had a bactericidal action even though it did not contain any complement. It is evident, also that certain of the maternal sera contained natural amboceptor although the sera of the offspring lacked this component.

In view of the experimental data which are recorded in the preceding sections, answers can be given to three of the questions which were asked in the introduction of this paper. The answer to the first question, namely, is the antibody content of normal maternal and newborn sera equal, is obvious. The maternal and newborn sera are not equal in their bactericidal action, and the value of the maternal serum is always much higher than that of the newborn. This result is in agreement with that of Halban and Landsteiner,[45] Schenk[88] and other investigators.

Some variation was observed in the bactericidal action of the sera of the adults, but it was impossible to demonstrate any variation dependent upon or associated with pregnancy. The values of the sera of nonpregnant women and of men were about equal to those found in women in the various months of pregnancy or at the termination of the second stage of labor.

It may be assumed, therefore, that the difference in bactericidal action is due to a deficiency in the antibody content of the serum of the newborn and not to an increased activity of the maternal serum. This conclusion answers the questions relative to the possible explanations of the difference in the bactericidal values of the two sera, but the last question—what is the process by which natural immunity is developed?—will be considered in a following paper.

(Note.—Bibliography will be found at the end of the second paper which will appear in the August issue.)

THE DIAGNOSIS OF STERILITY IN THE MALE AND FEMALE*

By Max Huhner, M.D., New York City, N. Y.

I HAVE purposely limited this paper to *diagnosis*, as accurate diagnosis, by which I mean the discovery of the actual seat of the trouble, is essential to scientific treatment. The time is, or should be passed, when the word "sterility" was considered a diagnosis in itself, without further investigation. Just as in urinary lithiasis, we are not satisfied in saying that the patient is suffering from calculus, but we must know exactly in what portion of the genitourinary tract such calculus is, before operating. So in sterility, we must know not only whether the male or the female is at fault or both, but also we must endeavor to determine in what part of the anatomy of either sex the impediment lies, before commencing treatment.

One of the oldest methods of determining the fructifying ability of the male is the examination of a condom specimen. There is no doubt that this gives valuable information, but it has its distinct limitations which must be taken into account in making a diagnosis. These limitations will be elaborated in detail later.

The examination of a condom specimen must be performed in a definite manner or else the whole examination may come to nil. The condom after removal from the organ must be tied with a string to prevent its contents from spilling en route. This statement may seem superfluous, but experience has taught me that unless the patients are definitely instructed, they are very apt to tie the condom by making a knot with the loose part of the condom itself. This, in many cases becomes unloosened and the contents are spilled.

There are some specialists who advise placing the condom in warm water to keep the spermatozoa alive en route. I would most emphatically advise *against* any such procedure. It is true that the expert bacteriologist or chemist can tell with or without a thermometer what the temperature of the water is, but our patients are not bacteriologists or chemists, and in their endeavor to have the water hot enough, will, in the vast majority of cases, make it too hot, thus killing off all the spermatozoa. It must be remembered that while spermatozoa will stand some cold, the least amount of heat above normal will kill them immediately.

The method which I have recommended for many years is very simple and efficacious. As soon as the condom has been tied as directed, it should be placed between the warm bed pillows until

*Read at a meeting of the Harlem Medical Association, December 5, 1923.

ready for transportation. A large towel should also be placed between the same pillows. As soon as the patient is ready to come to the office, the condom should be placed within the towel and the entire package placed as near the body as possible to keep it warm during transportation. This precaution is especially necessary during cold weather.

When the specimen arrives at the office, it should not be exposed until everything is in readiness for examination. Microscope, slides, cover-glasses, etc., should all be ready. For examination of semen, only an ordinary microscope with high and low power lenses is necessary. There is no need of warm-stage apparatus, or anything else to preserve the specimen during examination. There is no special art or experience necessary for such examination, and any general practitioner should be able to examine a condom specimen.

When everything is in readiness, we may proceed to procure the specimen. I have always found that the more complicated the method, the more the specimen is poured from dish to dish, the worse the result. The only instrument I employ is a large pipette.

I untie or cut the cord with which the condom is fastened, insert the pipette, suck up the contents of the condom, allow the first drop to escape, and then deposit a drop on the slide, and cover with the cover-glass. While examining this specimen, I enclose the pipette in a towel, in order to keep it warm in case more specimens are required. Nothing can be more simple or more efficacious than this procedure.

The general appearance of the field should be noted, first using the high power. In a normal specimen, innumerable spermatozoa are at once seen dashing very rapidly about the field. Whenever one has to search for spermatozoa, it shows that the semen is abnormal. There are no two ways about it, either one sees them at once or one does not. Staining is not advisable.

If, instead of the above picture, however, we see at once many Böttcher's crystals, we can immediately decide that the semen is abnormal. In this case, the spermatozoa are either greatly diminished in quantity, or are dead, absent or moving very feebly. An occasional crystal can be seen in normal semen, and if normal semen is examined after the spermatozoa have all died, we will also find them in large quantities. It is the *early* finding of a large quantity of these crystals that stamps the specimens as abnormal.

The theory of the formation of these crystals is as follows: A moving fluid does not crystallize, or does so very slowly. In semen containing many moving spermatozoa, therefore, the crystals either do not form at all, or do so very slowly, whereas they are formed

rapidly and in large numbers in semen containing either no spermatozoa or only dead ones.

In these cases, in which repeated condom examinations, after long periods of continence, persistently show no spermatozoa at all, we have by no means done our duty to the patient by telling him he is sterile, and perhaps advising some operation on the epididymis. We must determine whether the absence of spermatozoa is due to an obstruction in the epididymi or vasa, or whether it is due to the fact that the testicles themselves do not manufacture spermatozoa, or to both conditions combined. It is perhaps unnecessary to state that the testicle has two distinct and independent functions, one, the spermatogenic function, and the other the secretion of a hormone which determines the secondary sexual characteristics of the man. Either function may be destroyed without interfering with the other. On the one hand, we have the person, who is manly in every respect, with normal sexual desire and power, with normal secondary sexual characteristics, yet whose semen contains absolutely no spermatozoa. On the other hand we have the invert, with no sexual inclination towards a female, but marked libido towards one of his own sex, with many marked feminine characteristics, yet when he marries, as he sometimes does for economic or other reasons, he is able to impregnate his wife and bring forth progeny.

It is with the former of these types that we have to deal. To advise an epididymo-vasostomy simply because no spermatozoa are found in the semen is absolutely unjustifiable. The condition may be either congenital or acquired. An attack of mumps, or a severe gonorrheal orchitis may produce the condition. How are we to diagnose this condition from azöospermia due to obstruction in the epididymi or vasa? It must be remembered that while the finding of a thickened condition of the epididymi is very suspicious of obstruction, it is not an infallible sign, for, not every thickened or nodular epididymis is obstructed. Furthermore, even if obstructed, it may not be the single cause of the azöospermia, for, in some cases of gonorrhea, not only is the epididymis attacked, but the inflammation is so severe that it takes in the testicle at the same time, completely destroying its spermatogenic function. Here again, epididymo-vasostomy or any other operation is doomed to failure. On the other hand I have called attention to a form of epididymitis or vasitis, in which there is not present the acute pain or swelling which accompanies the ordinary form of epididymitis, but in which there is just enough inflammation to cause an agglutination of the walls of the epididymis or vas. The patient never knows he had an epididymitis, there is not felt thereafter the hard thickened nodule so characteristic of a previous epi-

didymitis, but the obstruction is there just the same, and in case both sides are affected, absolute azöospermia results.

I have devised a method of differentiating these forms of azöospermia. It consists in aspirating the testicle and immediately examining the aspirated testicular fluid for spermatozoa. I have described the technic in detail in some of my other publications[32, 33, 36, 37] and will not repeat it here. I merely wish to mention that even in normal cases, the amount of fluid aspirated is very little, the number of spermatozoa found very small, and we may have to search for some time before finding any. Inasmuch as this is a paper on diagnosis and not on treatment of sterility, no detailed description of the treatment for these conditions is in order; I wish to remark, however, that in case spermatozoa are found in the aspirated fluid, our diagnosis is obstruction, and operation to relieve the obstruction is proper. In case no spermatozoa are found, no operation is indicated no matter how many nodules we find in the epididymis, but we may try to develop the spermatogenic function of the testicle by the administration of anterior pituitary lobe, which, at times brings about truly remarkable results.

Many pus cells in a condom specimen are distinctly abnormal, and if associated with absent, dead or feeble spermatozoa, we can, in a general way conclude that there exists some pathologic condition in the male sexual apparatus, which is responsible both for the pus cells and the abnormal semen, and which should be investigated. I have shown heretofore[32, 36, 37] that pus itself does not interfere with the vitality of spermatozoa but that it is the pathologic condition in the genitalia which is responsible for the sterility as well as the pus. That this is not merely theoretical is clinically proved by the fact that a man can at the same coitus impregnate his wife and infect her with gonorrhea, the gonococci and pus not interfering with impregnation.

It cannot be too emphatically stated that the mere finding of a few active spermatozoa, or the finding of many feebly moving spermatozoa, does not absolve the male from sterility. Many inexperienced physicians do not see the importance of this. It is so easy to say to the patient that it takes only a single spermatozoon to cause impregnation, and as long as the specimen shows one live spermatozoon, impregnation is possible. When we consider, however, that with each normal ejaculation there are thrown into the female genitals more than three hundred million spermatozoa, in order that one shall reach the ovum, it is easy to calculate the chances of impregnation when only a few lively ones are ejaculated.

The finding of only dead spermatozoa in the semen is generally considered of no importance, whereas it has great diagnostic value. It tells us at once that there is no obstruction either in the epididymis

or vas, and that epididymo-vasostomy, the operation of anastomosing the epididymis and vas, is absolutely contraindicated in such a case. In these cases it must be determined by careful examination of the seminal vesicles, prostate and urethra, just where and what kills the spermatozoa. In such cases also one should make his own condom examination and not rely upon the report of a laboratory or other physician. One should also carefully inquire from the patient just how he collected and preserved the specimen, for at times, in spite of careful instruction, the patient may have slipped up in some detail, and caused the death of the spermatozoa after ejaculation.

Immature and deformed spermatozoa are occasionally found in a condom specimen. These are probably useless for purposes of impregnation, but do no harm and are occasionally found in perfectly normal semen. The main point in determining the fructifying power of semen is the finding of a large number of actively moving spermatozoa in every field. This is all we can expect to determine from the examination of a condom specimen. The viability of the spermatozoa in the various secretions of the female genitals, and their actual value for purposes of impregnation cannot be determined by any chemical or physical test of the specimen itself, nor can any conclusion be drawn from the behavior of spermatozoa from such a specimen under the microscope, but only by the "Huhner Test" presently to be described. I purposely desire to emphasize this point because there are some observers who have tried, and actually recommend the timing of the rapidity of motion of spermatozoa from a condom with the aid of a stop-watch, and base their valuation of the semen from such observations. Others have recommended the observance of how long spermatozoa will remain alive under the microscope. For many years I have protested against all these tests because they are not only not practical, but also because they are unreliable. What do we care how long spermatozoa live under the artificial conditions of the microscopic stage, as long as we can determine absolutely accurately how long they live, if at all, in the female genitals. Surely for practical purposes the latter deductions are of greater value than the former. Moreover, with the "Huhner Test" we test the vitality of the husband's semen in the genitalia of his own wife, which itself is of the most important practical diagnostic value.

Nor can we make any reliable deductions from how long spermatozoa remain alive under the microscope. Many times have I removed live active spermatozoa from the female cervix *several* days after coitus, only to see them die very rapidly under the microscope. Were we to make any deductions from their rapid death under the microscope, we would put them down as of very poor quality, whereas

the fact that they have lived several days in the female genitals, shows them to have been of very excellent quality.

Before describing the Huhner test, there is just one more point to which I desire to call attention. It often happens that single males, about to be married, are anxious to find out if they are sterile. This applies more particularly to those having had gonorrhea, and especially epididymitis. Of course we could advise them to indulge in coitus using a condom, and thus procure a condom specimen, but such advice ought not to be given. It has been my custom for many years, to have such patients call at my office with a full bladder, and as long as possible after a pollution. I then rather vigorously massage the prostate and strip the seminal vesicles until some of their secretions appear at the meatus, which I examine at once for spermatozoa. The amount of secretion appearing at the meatus varies greatly within perfectly normal limits. In some cases the fluid thus examined shows almost as many lively spermatozoa as a condom specimen, while in other cases very few are found. Both conditions are absolutely normal. The patient must be informed before such examination is made, that while the finding of live spermatozoa in a specimen obtained in this way, shows that the testicles are working properly and that there is no obstruction in the genital ducts, the absence of spermatozoa does not by any means indicate that the patient is sterile. In a condom specimen, as before said, it is imperative to find many active spermatozoa, but in a specimen obtained by expression from the prostate and seminal vesicles, their absence does not indicate anything pathologic. We simply cannot draw any conclusions. I have repeatedly found them absent in married men who were fathers of several children. Even if found, we must be careful not to make any statement guaranteeing offspring to the candidate for marriage. All we can say is that if the normal spermatozoon comes in contact with the normal ovum of the female, and no genital impediment exists in the female, impregnation will probably take place; but there is nothing in the appearance or action of the spermatozoa under the microscope which will tell you whether they will survive in the female genitals long enough to reach the ovum.

I have said that there are certain distinct limitations to the diagnostic inferences which can be drawn from the examination of either a condom specimen or one procured from manipulations of the prostate and seminal vesicles. The limitations have been gone into with much detail in other publications of mine[32, 33, 34, 35, 36, 37] so that only the conclusions will be mentioned here. In the first place, we cannot in any case be sure that the spermatozoa will ever reach the cervix and fundus, or even the interior of the vagina. Take a case of hypospadias or epispadias; the condom specimen will be absolutely normal

yet, on account of the abnormal urethral opening, the fluid may be ejaculated entirely away from the cervix, or even outside of the vagina. As another example, we may mention a tight stricture of the urethra; here again, the condom specimen will be all that can be desired, but, on account of the stricture, the fluid is not at all ejaculated, but dribbles out of the meatus after the organ becomes flaccid. As another and very common condition, take the cases of partial impotence, with very rapid or even premature ejaculation. Here again, the condom specimen may be normal, but, on account of the weak ejaculation, the semen is deposited far away from the cervical os, at the very entrance of the vagina, or, in particularly bad cases, ejaculation takes place before penetration. Among other conditions showing a normal condom specimen, but in which the semen does not reach the cervix, may be mentioned abnormal positions of the cervix itself, awkward coitus, etc. Time will not permit me to mention every condition, so only the more common and obvious have been referred to.

Another serious limitation to the condom test is, that even if the spermatozoa get into the wife's genitals, there is no way of telling whether they will survive there. I cannot lay stress upon this point too emphatically, that, no matter how active or normal spermatozoa appear under the microscope, there is no way of telling from their appearance or action, that they will live in the various secretions of the female genitals. Moreover, a chemical examination of the female secretions, will also not give us any reliable data. Various experiments have been tried in both these directions, but little progress has been made. Besides all such tests are not only time-consuming, but require the services of an expert chemist, and are totally unfit for general use.

It was such limitations in our diagnostic ability with condom specimens that induced me, many years ago, to make a series of experiments and observations upon the behavior of spermatozoa within the female genitals. These observations extended over a period of six years, and culminated in a test for sterility which I called the "Spermatozoa Test," but which subsequent writers have called the "Huhner Test," and it will so be designated in this paper. The test is simplicity itself, and gives us such a fund of information regarding the diagnosis of sterility, and eliminating the disadvantages and limitations above referred to, that I make no apology for presenting it at some length. I hope the time has passed when the physician examined a drop of semen from a condom, and finding normal spermatozoa, immediately told the husband he was all right, and placed all the blame on the female.

All that is required for the test is any sort of pipette, and some

form of intrauterine syringe in case we desire to obtain specimens from the fundus.

The woman comes to the office as soon after coitus as possible, is placed in the ordinary gynecologic position, a bivalve speculum is inserted, the cervix is brought into view, and some of the cervical contents is sucked into the pipette, and immediately expelled on a slide and examined under the microscope. Often we at once see numerous lively spermatozoa, yet what a wealth of information is obtained from this few minutes' examination! What do we care whether the cervix is in its normal position or not, or whether we could reason out theoretically that, during coitus, the penis goes into this culdesac or that, whether the vagina is very short or of excessive width or depth—*the living spermatozoa on the cervix tell us at once, that for that particular penis, the cervix is in the right position to catch the semen.*

I do not wish to report cases, as it would unduly lengthen this paper. I cannot refrain, however, from citing a recent case, which is not at all uncommon. A woman who had been sterile, though married several years, came, by appointment for the Huhner test. The examination disclosed a large pool of semen in the posterior fornix, but the uterus was markedly retroverted, so that the cervix pointed directly upwards towards the abdomen, entirely away from the seminal pool. The entire fundus lay in the seminal pool instead of the cervix. Were we to reason from the gynecologic examination, we would certainly conclude that the sterility was due to the position of the cervix, which was away from the seminal pool. Yet the Huhner test showed the cervix simply swarming with live spermatozoa, showing conclusively that the position of the cervix had nothing to do with the sterility. In this case, the Rubin test subsequently showed both tubes occluded. In previous years, before it was so easy to determine the permeability of the tubes, and without the Huhner test, this woman would have been subjected to all sorts of operative procedure to correct a condition, which had nothing to do with the sterility.

Every year, I see many patients in my office who have been advised by their physicians to assume unusual positions during coitus with a view of aiding the spermatozoa to reach the cervix. This question is solved at once with my test. Again, we do not care if the woman tells us that she does not become pregnant because all the semen runs out of the vagina immediately after coitus, for we have positive proof before us (in case we find living spermatozoa in the cervix) that, no matter how much runs out, enough spermatozoa have reached the cervix for purposes of impregnation. What need we care, if informed that the husband suffers from rapid ejaculation, for again,

we have positive proof before us that he can deposit his semen in the right place. Similarly, we need not worry about many other conditions which are commonly supposed to be the cause of sterility, such as diminution or absence of orgasm in the woman, stricture of the urethra, epispadias, hypospadias and other conditions in the male, for we have found live spermatozoa in the cervix, and we therefore know that none of these conditions has any influence in this case of sterility.

Likewise we need not worry over the possibility of the cervical or vaginal secretions being inimical to the vitality of the spermatozoa, nor need we subject these secretions to chemical examinations, for again we know that they cannot be the cause of the sterility in this particular case. And so we may go through many of the theoretical ideas as to the etiology of sterility, and see how frequently they are dismissed as the result of this few minutes' examination. I may perhaps be pardoned for my enthusiasm concerning the test, but I really know of no other test from which so much valuable information can be gained in so short a time.

Suppose, however, that only dead spermatozoa are found in the cervix. We then examine a condom specimen, and if it contains only dead spermatozoa, we know the fault is with the husband; if live spermatozoa, however, are found in the condom, we know at once that something about the genital secretions of the female has killed the spermatozoa. Again we do not need to submit the secretions to time-consuming chemical and microscopic examinations to arrive at this conclusion, for we have the *physiologic* proof before us. In this condition, if we find the vaginal or cervical secretions markedly acid, we order a bicarbonate of soda douche before coitus, and make another test. If this second test now shows live spermatozoa in the cervix, we have not only made our diagnosis, but have been informed how to preserve their vitality and cure the sterility.

If no spermatozoa at all are found in the cervix, the husband may still be at fault, even though live spermatozoa are found in the condom. This is one of the most important practical features of the test. Ordinarily, a normal condom specimen was considered absolute proof that the husband was not responsible for the sterility. A gynecologic examination was then resorted to, and any slight deviation from the normal was at once seized upon as being the cause of the sterility, and the wife was subjected to prolonged treatment and even operation. Yet the husband may be suffering from urethral stricture, epispadias, impotence or any of the other conditions previously mentioned under the limitations of the condom test. In this case we request a condom specimen, and if it contains live spermatozoa in sufficient quantity, we must conclude that though the

semen is normal, he is unable to deposit them in the female genitals, and any of the previously mentioned pathologic causes which may induce this phenomenon is investigated. If, however, the condom does not contain any spermatozoa, the diagnosis is obvious, and our energy is directed towards finding the cause in the male as previously pointed out.

But the diagnostic value of the test is not limited to the cervix. We may look for spermatozoa as high up as the fundus uteri. At first blush this seems impractical, as, whatever specimens we obtain from the fundus are bound to be contaminated with those from the cervix. This objection, however, can be overcome by making the examination several days after coitus, at which time those spermatozoa which have been deposited in the vagina and cervix have already died. To make certain of this fact, we may, at the examination first take specimens from the cervix and vagina, and if these specimens show only dead spermatozoa, or none at all, and, with an intrauterine syringe we can suck out live spermatozoa from the fundus, we can be certain that these could not have come from below. The minute details of this method of examination, have been published in some of my former works[32, 33, 34] and will not be repeated here. Of course, the later after coitus such examinations are made, the more difficult it is to find spermatozoa. If we do not find any spermatozoa at all in the fundus, we cannot draw any conclusions, as they may not be found even in normal cases. The test therefore, as far as the fundus is concerned, is only of value if spermatozoa are found.

But if we find live spermatozoa in the fundus, what great diagnostic wealth is revealed to us! How many women have been subjected to prolonged treatment and operation because an anteflexion was supposed to interfere mechanically with the ascent of the spermatozoa! How many women have been curetted because it was believed that the endometrium was inimical to the vitality of the spermatozoa! To the credit of the modern gynecologist be it said that these operations are not indulged in with anything like the frequency of former days, but the general practitioner has not yet learned this lesson. There is hardly a case of sterility which comes to me in which at least one dilatation and curettage has not been performed, and many of my patients had submitted to several of these procedures. The finding of live spermatozoa in the fundus at once shows the folly of such procedures in that particular case.

In these cases of sterility in which live spermatozoa are found in the fundus uteri, our diagnosis is narrowed down to one of three conditions: (1) a small, undeveloped or infantile uterus which will not nourish a developing impregnated ovum; (2) obstruction in the

tubes; and (3) condition of the ovaries, endocrine or otherwise in character.

The first can easily be diagnosed by vaginal examination. If we find a small undeveloped uterus, in a sterile woman and no other pathologic condition present, we may reasonably conclude that this is the cause of the sterility, and, in my experience, it is a very common cause. I must, however, warn at jumping at the opposite conclusion, namely, if on routine examination we find a small uterus to prophesy that the woman will be sterile. I have repeatedly examined women shortly after marriage for other complaints, and have found a very small uterus, and yet the woman conceived and gave birth to children.

Obstruction in the tubes can now be positively diagnosed by the Rubin test. The technic is very simple, entirely harmless, practically painless, and can be done in the office or dispensary, the patient going home shortly afterwards. The test should be made a routine just like the examination for spermatozoa.

The third condition, insufficient ovarian secretion as the cause of sterility, can be considered almost certain in those cases where we find an infantile uterus, together with late onset of menstruation, scanty menses, and menses coming on at very infrequent intervals, say only three or four times a year. To this syndrome is sometimes added lack of sexual desire, but, inasmuch as this latter symptom is very common in fertile women, it has little weight as a diagnostic phenomenon. Here we have a distinct endocrine disturbance, in which, in all probability, the other endocrine organs are also disturbed with the ovaries. Many of these cases are congenital in origin, or owe their onset to some disturbance prior to puberty. Endocrine treatment is distinctly in order, and I have had some remarkable results in this class of cases with corpus luteum extract.

Ovarian sterility may also be due to ovarian cysts, corpus luteum cysts, thickening of the tunica albuginea, thus preventing follicular rupture, etc. In these cases, the direct disturbance is also in many cases, endocrine in character, but the cause of the endocrine disturbance is found in local pathology. In some cases a pathologic condition in one ovary will cause endocrine disturbance in both ovaries. Many of these cases can only be diagnosed by exclusion, and some only by laparotomy.

Finally, in some cases there exists a disharmony between the spermatozoa of the male and the ova of the female. In these cases, both parties can produce offspring with different mates. Although some experiments have been made by testing the serum of the female against the spermatozoa of the male, no definite conclusions have thus far been arrived at, and no diagnostic aid has resulted from these experiments.

There are other forms of sterility which have not been touched on in this paper, because they are still in an experimental stage. Among such forms may be mentioned sterility due to a deficiency of certain chemicals in the blood, which is sometimes cured by putting the patient on a particular diet containing an excess of the deficient material. Sterility may be produced in animals by injecting male sperm into the blood of the female. By analogy this phenomenon is supposed to explain certain forms of human sterility, in which it is suggested that the sterility is due to the absorption of spermatozoa or their products by the female through her genitals.

I have thus shown that by a careful study of our sterile patients, we can, in the vast majority of cases, lay our hands directly on the offending organ or function in either sex. In conclusion I merely wish to mention one important caution in the diagnosis of sterility. In every case where a patient had submitted to a laparotomy, no matter for what condition, get in touch with the surgeon or hospital and find out the details if possible. If often happens that a gynecologist will, for perfectly justifiable reasons, remove both tubes, or one tube and the opposite ovary, without informing the patient what was done. At times the surgeon is afraid of a possible law suit, or he may think it too depressing for the patient to know that she is hopelessly sterile. In my experience, I have had not a few such patients consult me for sterility, whose histories showed that they had made the rounds of several general practitioners, even submitting to curettage or cervix operations for a sterility that was incurable, due to a previous operation. I remember one case which had submitted to various treatments for a period of ten years before seeing me, and upon investigation, I discovered that she had had both tubes removed for a tuberculous salpingitis. In some of these cases the Rubin test will show that the trouble lies beyond the uterus, but the exact diagnosis can only be obtained from the laparotomist.

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320 Central Park West.

THE INTRAUTERINE CONTRACEPTIVE PESSARY—INEFFICIENT AND DANGEROUS

By R. S. Siddall, M.D., Detroit, Michigan

(From the Obstetrical Department of the Henry Ford Hospital.)

NOTWITHSTANDING all attempts to suppress the birth control movement, the fact remains that considerable information and misinformation regarding contraceptive means have been disseminated among the public. On the other hand, it is well known that most members of the medical profession recognize certain disease conditions as contraindications to pregnancy and their presence as sufficient justification for the recommendation of contraceptive procedures. Various devices have been developed for both professional and illegitimate use, but, although many are inefficient and others are harmful, there is very little specific information in the American literature on the subject, a situation which no doubt has led to the widespread adoption of uncertain or harmful methods. However, the matter has been studied and presented in the foreign literature, especially in Great Britain and Germany, and the facts seem to be established in regard to at least one contrivance, namely the intrauterine contraceptive pessary.

It is stated by Pust that in Germany the various models of this type of pessary are among the most commonly employed means for preventing pregnancy. In this country it is not uncommon to see them and to be called upon to treat illness which has resulted from their use. It is interesting to note that this is the method which one of the leading proponents of birth control in this country is said to recommend as being both certain and harmless. It would seem, however, that she is mistaken in both respects, and it is regrettable that so many have been influenced without further investigation to use this pessary. The following case report is illustrative of the inefficiency of the method:

H. F. H., 26966, white, aged twenty-seven, married in 1917. The patient was first seen at this Hospital on March 20, 1923, and the essentials of the remote history taken at that time were as follows: She had never been ill except for the usual exanthemata of childhood. Since the age of twelve she had noticed a swelling in the region of the thyroid gland which had since increased gradually in size, especially with pregnancy. Upon direct questioning no history of symptoms referable to hyperthyroidism was obtained. In 1919 and again in 1921 she had been delivered by spontaneous labor of normal children, and in March, 1922, there was a spontaneous abortion of an early conceptus.

Soon after the abortion in March, 1922, the intrauterine contraceptive pessary (described below) was introduced by a physician. In September, 1922, she stated that, when about two weeks past the expected time of menstrual period, there had been severe bleeding for ten days with temperature up to 104° and the expulsion of several small blood-clots,—no doubt an early abortion. The next and last menstrual period occurred on November 24, 1922. Soon afterwards nausea and vomiting developed and the patient believed she was pregnant. For several months she had noticed more than the usual dyspnea upon exertion.

Examination on March 20, 1923, confirmed the history as to the existence of pregnancy, the size of the uterus corresponding to the menstrual history. The disc of the pessary was held tightly against the tip of the cervix by tissue which had grown down through the ring, and considerable difficulty was experienced in its removal. Following this there was a thick mucous discharge and slight bleeding but no serious results. On general physical examination a well compensated mitral stenosis and insufficiency was noted. There was also rather marked diffuse enlargement of the thyroid gland but no definite signs of hyperthyroidism. The blood Wassermann was negative with plain, cholesterinized, and Kolmer antigens.

The pregnancy progressed uneventfully, the blood pressure never going above 120, the urine never showing albumin, sugar, or casts, and the heart condition remaining satisfactory. On September 17, 1923, sixteen days past the calculated expected date of confinement and after the administration of castor oil and quinine sulphate, the patient had an easy spontaneous labor with the birth of a normal child. The puerperium was uneventful, and at the end of two weeks both mother and child were discharged from the hospital in excellent condition. On microscopic examination the placenta showed nothing abnormal except white infarcts, and the umbilical cord was normal.

Description of the Pessary.—This pessary is apparently made entirely of gold which is labeled "14 K," and weighs three grams. The part which fits over the tip of the cervix is 2.5 cm. in diameter and concave on the surface next to the cervix. In the middle there is a hole 1 cm. in diameter, and across this a narrow bridge of metal which supports two upright wires 5 cm. long. These are encased in a small wire coil for a distance of 2 cm. from the button, and it is this part which occupies the cervical canal. Above the coil the two upright wires extend for 3 cm. and are widely separated, each ending in a pear-shaped head. These parts by their spring effect pressed against the lateral uterine walls and served to retain the contrivance in place. Obviously the pessary could not be expected to protect the cervix mechanically from the entrance of spermatozoa since the external os was exposed through the hole in the cervical cap.

The various modifications of this intrauterine pessary were discussed at length at the Dresden Gynecological Society meeting in May, 1921, and its uncertainty and ineffectiveness were evidently common knowledge among those present. Rübsamen stated that a few days previously he had removed such a pessary from a woman then in the second month of pregnancy, and Richter mentioned several similar experiences. Royston (1923) reports the delivery of a woman at term following the removal of a pessary when she was three months pregnant. McIlroy of London believes that the device favors rather than prevents pregnancy.

As can well be understood, the introduction of such an instrument into a uterine cavity in which a pregnancy already exists would very

probably lead to abortion. Kehrer stated that he had repeatedly seen this as an accidental or intentional result.

Probably the most important argument against the use of these pessaries is that they are irritating to the endometrium just as are other intrauterine pessaries or foreign bodies. Kehrer says that they set up inflammatory reaction after remaining in for as short a time as one week. He and Prüsman, and West in this country, have seen severe endometritis, salpingitis, parametritis, and pelvic peritonitis as a direct result of these irritating foreign bodies, and Abbott-Anderson reports that death has occurred in several instances. Albert, Richter

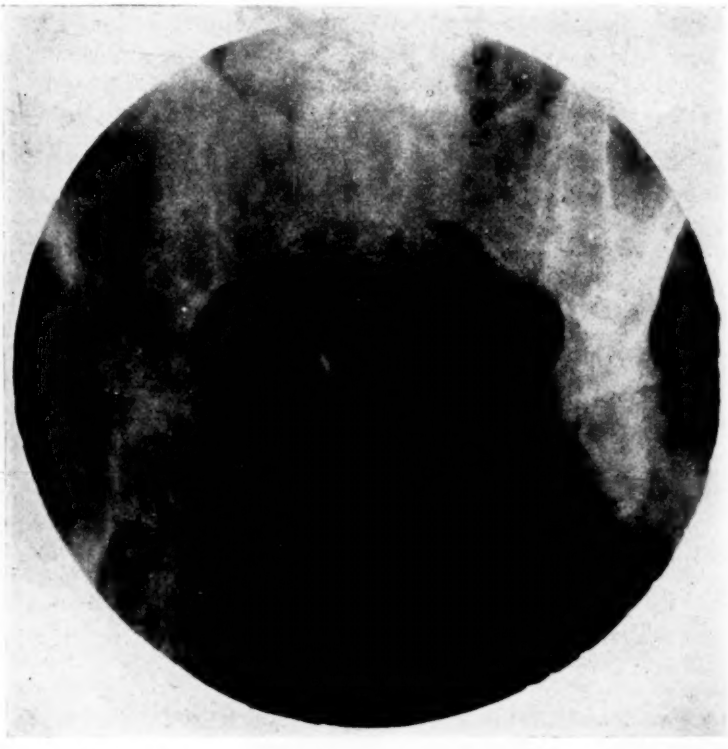

Fig. 1.—X-ray of pelvic region before removal of contraceptive pessary.

and Barrett state in no uncertain terms that there is grave danger in their use. On the other hand, Pust thinks that the intrauterine part of his contrivance, which is made of silkworm gut partly wound with silk, is not irritating. However, Kehrer states that he has seen severe endometritis from silkworm gut sutures, and Haire believes this type to be open to the same objections as the other forms. Indeed, it is believed that none of these devices do much towards preventing conception, but rather do they promote early abortion by reason of the endometritis which their presence has induced. Such, perhaps, is

the explanation for the early abortion in the case outlined above. Certainly, the temperature elevation indicates that severe infection was present.

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GYNECOLOGIC PLASTIC SURGERY UNDER SACRAL-TRANSSACRAL ANESTHESIA*

BY M. O. MAGID, M.D., AND WILLIAM KLEIN, M.D., NEW YORK, N. Y.

WHILE plastic gynecologic surgery may not be classed as emergency surgery and may be omitted, if organic lesions exist in the patient that preclude the use of a general anesthetic, there are many cases where a plastic gynecologic operation would relieve a patient of constitutional symptoms, as with a focus of infection in the cervix, and from discomforts due to an extrusion of the bladder or rectum or both, and finally with various degrees of prolapse of the uterus caused by a loss of support of the pelvic floor.

Plastic surgery in gynecology may therefore be included as a necessary practice for relief. In order that we should be able to operate on those cases in which a general anesthetic might be a source of danger, different types of regional anesthesia are being practiced, with the idea of perfecting such a method under which these operations may be made as nearly painless as they would be under a general anesthetic.

The object of this paper is to present a report of a series of cases operated on at the Bronx Hospital under sacral-transsacral anesthesia, with the hope of encouraging other surgeons to use this method, that their patients may be spared the discomforts and possible added shock of a general anesthetic.

There are certain advantages of sacral-transsacral anesthesia, which is an improved method of all other forms of nerve block, over general anesthesia, in that there is a lowered immediate and remote risk to operation. The possibility of lung complications is eliminated. Nausea, vomiting and thirst are absent. Instead the patients are comfortable in every way and may be fed a fairly good meal, several hours after the operation. Another advantage is that liquids may be given to the patients during the course of the operation.

*Read before New York Physicians Association, November 28, 1923.

While both local anesthesia with scopolamine and spinal anesthesia methods as well as nerve block have been used in cases of so-called "bad risks," the time has come when, with perfected technic, we use spinal anesthesia and its modifications, in cases that are "good risks," i.e., patients who are physically able to stand a general anesthetic, but dread the idea of being rendered unconscious and prefer block anesthesia. These patients are easily controlled by morphine and scopolamine, in such doses that will obtund their sensibilities to a degree that they are unconscious of their surroundings and yet are able to respond to questions.

In our series of cases we have twelve patients on whom tracheloplastic operation was performed, also operations for rectocele and

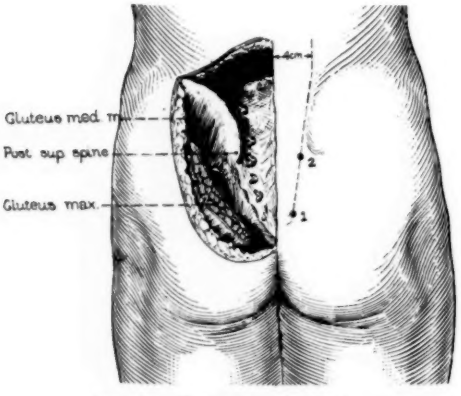

Fig. 1.—Transsacral block. The superficial landmarks in relation to the posterior sacral foramina. (Labat.)

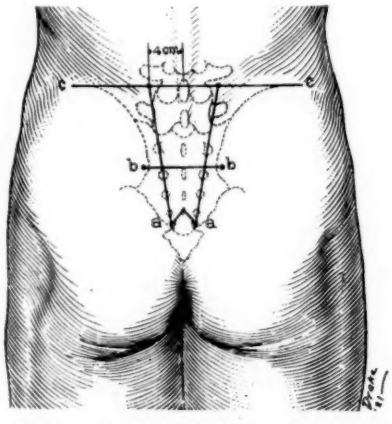

Fig. 2.—Transsacral block. Tracing of the lateral rows of sacral foramina on skin surface; *a, a,* are the sacral cornua; *b, b,* the posterior superior iliac spine; *c, c,* line tangent to the highest points of the iliac crests. (Labat.)

cystocele; two were operated for rectocele and cystocele, and one for rectovaginal fistula. The ages varied from twenty-seven to sixty-eight years.

The technic of the operation on the cervix and perineum was that described by Sturmdorf. The outstanding features of these procedures are that the dissection on the cervix is deeper and more extensive than that of the Emmet, Sims, or Schroeder operations. In the latter, the denudations are superficial. They do not require as much traction on the uterus as is necessitated by the tracheloplastic operation, especially when the sutures are inserted. It is at this point that the patients experienced a little discomfort. They did not complain of pain but were conscious of a dragging down sensation, which lasted only a few minutes, caused by traction on the uterus while the Peaslee needle was forced through the uterine tissue just above the

internal os. At one more step of the operation, the patients moaned. This was when the cervical denudation reached the culdesac. When the finger was inserted between the denuded cuff and the uterus and traction was made on the posterior flap, some discomfort was experienced. The complaint was not of pain but of a dragging sensation.

The levator myorrhaphy in every case was entirely without any complaint. In each case the vaginal mucous membrane was denuded until the levator ani muscles were exposed. These were sutured together with catgut. The mobilization of the levator muscles necessitates deep dissection. This was accomplished without any pain or discomfort.

In this series we used the combined method instead of either the sacral or transsacral method, either of which might have sufficed in a limited number of cases for the following reasons: With the combined method the anesthesia is of longer duration; in not a few sub-

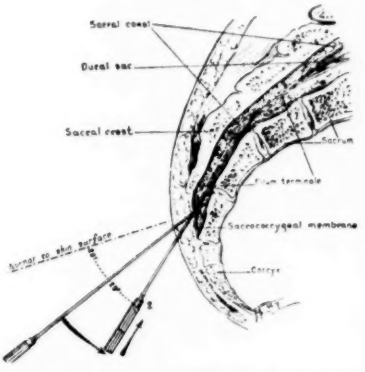

Fig. 3.—Sacral block. After piercing the sacrococcygeal membrane the needle impinges on the anterior wall of the sacral canal and passes from position 1 to position 2 in the direction of the arrows. (Labat.)

jects the posterior segments of the sacrum fail to close, in which cases the anesthetic is deposited in the ligament and a complete anesthesia is not obtained when the sacral block alone is employed. Again, with a transsacral block alone, it has been found that the sacro-coccygeal plexus is at times not well anesthetized.

The anatomy of the sacrum and of the coccyx has been omitted for obvious reasons, but a few important points are pertinent for the sake of clearness. The upper part of the sacrum is at a considerable distance from the overlying skin. This varies from 4 to 8 cm. and decreases as we descend. The first sacral foramen proper has a depth of about 2 cm., the rest of the foramina decreases by a half cm. The last or fifth nerve emerges just beneath the sacrococcygeal membrane.

A Labat syringe was employed, but any good Record syringe with well-fitting needles of the desired length will do. The solution used

was 1 per cent novocaine-adrenaline. Forty-five minutes before the operation, a hypodermic injection of morphine sulphate gr. ¼ and scopolamine gr. $\frac{1}{200}$ was administered.

The technic of the anesthesia as carried out by Dr. Wm. Klein of the Surgical Division of the Bronx Hospital is as follows:

The patient is placed flat on the abdomen with a cushion under the hips, thereby bringing the landmarks into prominence, also making them more accessible. The sacral hiatus is then defined by passing the tip of the left index finger from the end of the coccyx upwards along its prominence until just above the gluteal fold at which point a depression is felt. This marks the junction of the sacrum and coccyx. A ridge can be felt on either side of this depression; this being the cornu or lateral margin of the sacral hiatus. An intradermal wheal is made here. A needle 10 cm. long, preferably one with a bevelled stilet in it, with its bevelled edge turned upward, is introduced through the wheal at an angle of about 20 degrees. It is gently pushed forward until the sacrococcygeal membrane is pierced. We are then in the sacral hiatus. The needle is advanced until it comes in contact with the bone. It is then withdrawn about 1 or 2 mm. and the hub of the needle is bent downward towards the gluteal fold at an angle of about 40 degrees or more when necessary. The needle is then advanced into the sacral canal keeping in the midline until about 6 cm. have disappeared. It is a good plan to keep the tip of the left index finger at the point where the needle entered as it helps to steady the needle and to depress its proximal end when necessary. The stilet is then withdrawn and the hub of the needle is watched for spinal fluid or blood. If either is found to escape, the needle is withdrawn a little until the flow ceases. After all the air bubbles have been expressed, the syringe is attached to the needle, and the piston withdrawn a little to ascertain beyond all doubt that the injection is not made intravenously or into the intradural space. All details having been observed, 30 c.c. of the solution is then injected very *slowly* until most of the fluid is deposited. The rest of the fluid is slowly distributed while the needle is being withdrawn; the last few drops are deposited just beneath the sacrococcygeal membrane. A piece of sterile gauze is placed over this area. This completes the epidural injection, or sacral block.

For the transsacral block the patient is retained in the same position. The posterior superior spine of the ilium is located by passing the finger along the crest of the bone. In very fat subjects it can often be seen as a dimple or depression. A point about 1 cm. below and internal to it, indicates the second sacral foramen. This is marked with an iodine applicator. The sacral cornu on the same side is defined as previously described, and a similar mark is made indicating the fifth sacral foramen. A line is then drawn between these two points and an intradermal wheal is raised at either end. Two similar wheals are raised on this line at equal distances from both ends and from each other, dividing the line into three equal parts thus marking the third and fourth sacral foramina. At a point about 2.5 cm. above the upper end of this line and in the same general direction, i. e., upwards and slightly outwards marks the first sacral foramen, where a wheal is raised.

A needle about 10 cm. long is introduced perpendicularly to the skin and slowly advanced to a depth of from 4 to 8 cm. This will vary with the amount of adipose tissue encountered. When the needle makes contact with the posterior surface of the sacrum, it is moved about slowly until it is felt to sink to a deeper level. We are then in the sacral foramen. Here the needle is advanced not more than 2 cm. in the first sacral foramen. The same observations relative to

the possible flow of blood, as previously described, are made. If no blood escapes from the needle, the syringe is attached and withdrawn a little to ascertain its position as regards a blood vessel. Six c.c. of the solution is then injected. The same needle can be used for the second foramen, keeping in mind that there the needle must not be advanced to the same depth as the sacrum here is much more convex and therefore nearer to the skin. Here inject 5 c.c. of the solution. For the third foramen a needle half the length is sufficient and only 4 c.c. of the solution is injected. The fourth sacral foramen is again nearer to the surface than the third and the canal is only about 1 cm. long. Here 2 c.c. are injected. Finally, the fifth foramen is injected just beneath the sacrococcygeal membrane, 2 c.c. being deposited here. The same procedure is followed on the other side.

The anesthesia sets in immediately. The duration of the operation in the complete plastic cases averaged one and one-half hours, the tracheloplastic operation averaged about half an hour. The anesthesia continued for about an hour in some cases and a little longer in other cases, after the patients had been made comfortable in bed.

While it is not fair to assume that sacral-transsacral anesthesia is entirely comfortable to the patient, we believe that the slight discomfort which the patient might experience is well compensated by the knowledge that they have been relieved of maladies that have invalidated them for a number of years.

It is hoped that by perfecting the technic, which only comes after much practice and observation, even these slight discomforts will be eliminated.

EXPERIMENTAL ATTEMPTS TO PROMOTE UTERINE GROWTH*

By M. R. Robinson, M.D., F.A.C.S., New York, and Dr. B. Zondek, Privatdozent in the University of Berlin

FOR centuries preceding Brown Sequard's experiment, of injecting himself with testicular extract, in order to regain his lost vigor, physicians have employed glandular substances of animals as remedies for lost or weakened function of the corresponding organs, in the human. The clinicians of old, groped instinctively and intuitively through the devious trails of endocrinology; and we, with all the scientific means at our command, are still struggling to link theory to practice, with but slow, hesitating and faltering steps. We have learned to diagnose endocrinopathies with a fair measure of accuracy, but we have as yet not attained the same degree of efficiency in combating these disorders. The prevailing opinion, why our therapeutic successes with the endocrine preparations are not commensurate with the claims made for them by the manufacturers, is, that

*From the Universitäts-Frauenklinik der Charitè-Berlin. (Director: Geh. Med. Rat., Prof. Dr. K. Franz.)
This joint research was started during the winter of 1921 in the Universitäts Frauenklinik of the Charitè in Berlin and subsequently completed by Dr. Zondek.

these preparations either contain no "specific content" at all, or only part of the "active principle" of the particular gland in question. The past two decades have witnessed an intense activity on the part of biochemists and physiologists to isolate the active principles of the ductless glands, with astonishingly varied and contradictory results. Thyroxin, adrenalin, and pituitrin stand out at present as the triumphs of endocrine pharmacology, but recent information tends to weaken the solidity of even these few keystones in the foundation of organotherapy.

Hunt[1] claims "that for certain functions at least, thyroxin shows less potency than an equivalent dose of iodine in the form of the entire gland. So that thyroglobulin isolated from the glandular portion of the thyroid is not the active principle, but only one of the active principles of the thyroid."

Epinephrin, prepared from the medullary portion of the adrenal, is now claimed by Hartman[2] to be produced in the cortex of the gland, and that the medulla only serves as a receptacle for the secretion.

In the realm of gonadal therapy the confusion is still worse as will appear from the following survey of the recorded investigations.

A RETROSPECT OF OVOTHERAPY

The first clinical success with ovarian extract in a young person who suffered severely from the molimina of a surgically induced menopause was reported by Mainzer[3] of the Landau clinic, in 1896. As further trials with this preparation failed to give as brilliant results as originally recorded, investigations were set on foot to find and isolate the active principle or principles of the ovary.

Fraenkel's[4] researches led him to state that the corpus luteum is the important structure in the ovary which promotes uterine hyperplasia and causes it to undergo the cyclical histologic changes requisite for the nidation of the fertilized ovum.

Among American gynecologists, Burnam[5] was the first to report encouraging results from the use of fresh corpus luteum.

Loeb's[6] production of deciduomata, and Bouin and Ancel's[7] substantiation of Fraenkel's claim, that the corpus luteum is capable of producing hyperemia, congestion, and hyperplasia of uterine mucosa, seem to have furnished the conclusive proof, that this organ does promote uterine growth.

Following closely upon the above cited reports, Frank[8] published the result of his investigations in which he stated, that he failed to sensitize the uterine mucosa, or to bring about the deciduomata of Loeb, or the normal hyperplasia of the uterine mucosa, usually noted after follicular rupture, with subcutaneous or internal administrations of corpus lutem.

Adler[9] used watery extracts of the ovary and produced estrual changes in virgin guinea pigs and rabbits,—with corpus luteum extract, the hyperplastic phenomena were less noted. Schickele[10] experimented with castrated animals, and used watery and alcoholic extracts both from the ovary and from the corpus luteum, and could find no difference in the degree of edema, hyperemia and secretion of the genitalia produced by either of the extracts.

Iscovesco[11] has attempted to isolate the active principle of the corpus luteum by means of solvents which would retain the lipoid content. It was his conviction, that the vital ovarian hormone is bound up with the fatty constituent of the corpus luteum. He has also isolated a similar lipoid from the ovary, and found that both these extracts possessed similar physiologic and therapeutic properties.

Fellner[12] repeating the experiments of Iscovesco arrived at the same conclusion.

As the preceding experiments lacked chemical definiteness, Herrmann[13] set out to isolate an ovarian hormone that would fulfill these requirements. The result of his efforts was the production of a pentamine phosphate (N_5P_2), with which he could cause an enlargement and an hyperemia of the uterine horns in animals. Two years later he described this "active principle" of the ovary as a yellow, viscid easily volatile oil, which solidifies on cooling and gives a positive cholesterin reaction. He has also isolated a similarly potent principle from the placenta, which rendered equally good experimental successes.

Aschner[14] injected virgin guinea pigs with watery extracts of ovarian and of placental tissue, and has often obtained a marked growth of the uterus and vagina. The uterine horns reached the thickness of a finger, contained blood (hematometra) and the ovaries also showed evidences of stimulation. Corpus luteum extracts failed to give the same results.

Seitz, Wintz and Fingerhut[15] have isolated from the corpus luteum two lipoids: (a) luteolipoid (from old corpus luteum) which inhibits uterine bleeding and is indicated in cases of ovarian hyperfunction, and (b) lipamin (from fresh corpus luteum) which stimulates the uterus to hyperplasia, and is therefore recommended in functional disturbances due to ovarian hypofunction. Both these extracts are not soluble in alcohol, but are soluble in acetone and in ether, and are free from cholesterin.

Frank[16] in retracing the steps of preceding investigators came to the conclusion that the aqueous extracts contain little of the active principle, while the lipoids derived through alcoholic, ethereal, or acetone extraction, are most potent. And like Herrmann, he has found that the placental extracts obtained through similar methods yielded physiologic results, equal to those of the ovary. The most important fact in Frank's contribution is, "that the extract containing all of the fat soluble substances is by far the most potent." This fact has a vital bearing upon the pharmacology of organic *extracts, and furnishes the axiom, that, just as endocrinopathies are due to pluriglandular disturbances, so is the active principle of the ductless gland not contained in any singular portion of the gland, but in the gland as a whole.*

Matsumata and Macht[17] have further upset our recently gained knowledge about the physiologic effects of the ovarian and the corpus luteum extracts upon the isolated uterus. They were able to call forth contractions in the uterus with extracts derived from other glands and organs, and thus denied the specificity of the gonadal extracts.

Kohler[18] in 1915, and Esch[19] five years later, raised the question as to whether the hypodermic administrations of ovarian and of corpus luteum extracts constituted a specific therapy or a nonspecific protein treatment. Esch succeeded in getting as good, if not a better result, with subcutaneous injections of aolan and caseosan, as with extracts from the genital glands particularly in cases of metrorrhagia.

Wintz[20] recognizing the fact, that the various extracts and pressed juices derived from the endocrines do not represent the internal secretions in their true physiologic state, for decomposition and uncontrollable chemical changes take place in their preparation, conceived the idea of utilizing the liquor folliculi in its unaltered state, for therapeutic purposes. The results were far beyond his expectations. Fresh follicle juice and old follicle juice gave different reactions. The former had no effect

upon blood pressure, coagulation time, or upon the acceleration or diminution of the menstrual function. The latter on the other hand caused a rise of the blood pressure and hastened coagulation but had no local effects upon the genitalia. Wintz ascribes the potency of the old liquor folliculi to the formation therein of albuminoid split products.

Frank[21] continuing the experiments of Wintz, reported favorable results in causing hyperemia and enlargement of the genitalia in rabbits. Frank[22], refuting a misquotation by Allen and Doisy[23] states that "the ovarian hormone is no longer hypothetical and is not limited to the follicle fluid. It is contained in the follicle fluid and in the corpus luteum, probably also in the placenta."

This review of the literature for the past twenty-seven years proves how uncertain we still are about the vital hormone of the ovary. If watery extracts, alcoholic, ethereal and acetone solutions, cholesterin-free and cholesterin-containing substances, derived from the ovary, from the corpus luteum, and from the placenta, preparations so different in their anatomical derivation and in the method of production, are all capable of calling forth almost similar physiologic results, how can we claim specificity for any one of them? The hormonic theory is no longer an hypothesis, each ductless gland possesses a secretion peculiar unto itself, but the glandular preparations in the form of extracts and solutions as obtained in the market surely do not represent their physiologically active principle. Are there any preparations which do contain a true hormone, and if so which are they, and how may they be best produced? We shall attempt to answer this question.

PERSONAL EXPERIMENTS

That the growth of the uterus is dependent upon ovarian function is no longer doubted. Physiologically the uterus attains its normal size at puberty, which is denoted by the appearance of menstruation; it maintains these dimensions, with some slight increase during adolescence and maturity; at the beginning of senescence, involution and finally atrophy of the genital tract, take place, due to a sudden or to a gradual cessation of ovarian activity. Clinically we meet with the infantile uteri, acute anteflexions, dysmenorrhea, oligomenorrhea and sterility, when the ovary fails to function fully during the formative period of life; or we witness the psychic vasomotor disturbance of an artificially produced menopause, following operative removal of the genital glands. The hyperfunction of the ovary finds expression early in life in the phenomenon of pubertas precox, and later on in excessive periodic or irregular uterine bleeding. Every means therefore which will enable us to control and regulate ovarian function particularly in the direction of stimulating genital growth, will constitute a most valuable addition to the gynecologist's armamentarium.

In practice we are employing dry preparations, but chiefly extracts of the ovary. The experimental investigations which one of us,

(Zondek,[24]) has carried out upon the isolated heart, the uterus, and the small intestine, as well as upon the blood and upon metabolism, have shown that a *specific substitution therapy can only be accomplished* with either gland transplantation, or with a chemically pure endocrine derivative, but not with the broken up dry preparations. If the endocrine glands are subjected to a chemically schematic splitting up process, then we obtain extracts in which the active principle has been destroyed. Against these views are undoubtedly those manifold experiments which claim a specificity for the ovarian extracts. It thus became necessary to answer the following questions: (1) Is it possible to stimulate the growth of the genitals in virgin animals with the ovarian extracts? (2) Can this be accomplished with these extracts only, and how do the extracts of these glands act? (3) How do the nonspecific albuminous bodies and the albumin end products act?

Our experiments were carried out upon virgin guinea pigs, which at the beginning were of an average weight of 200 grams. It appeared to us, that in order to exclude the possible sources of error which limited experimentation most frequently entails, we ought to extend our investigations over a large series of animals. We also learned, as will be stated later on, from our control examinations, that the appearance of the genitalia, the state of their vascular distention, the succulence and the thickening of the uterine mucosa, are all dependent upon seasonal variations. All the animals were killed with chloroform, so as to further insure experimental uniformity. As to the estimation of the variations in the size of the organs, relative to our experiments, we became convinced that ocular inspection alone is misleading, even when the hypertrophy is very pronounced, and we have hence substituted a far more dependable guide, the torsion scale. All uteri were amputated at a level two mm. below the fusion point of the uterine horns, and after a close separation from the parametric tissues, they were excised together with the ovaries. The method is very simple, and the weight can be established with absolute accuracy. In order to form an idea about the state of other ductless glands, the spleen and the adrenals were also weighed and the kidneys examined.

According to our viewpoint the only dependable objective method by which the difficult problem of organic hyperplasia and growth can be proved without contradiction is by analytical weighing. Mere inspection, as already mentioned, is too uncertain a method for comparative studies, particularly if the examinations are made at long intervals of time, when the recollection of the previously seen uteri is already hazy. The microscopic findings, such as the thickness of the muscle and the mucosa, may also be misleading, unless the sections from the horns are taken at precisely the same level in all the specimens; a fact which can never be realized with absolute exactness. And

even if this were possible, the thickness of the uterine wall at the same level in a different animal of the same species is subject to wide variations.

The weight determination of the uterus and the ovaries proved to be quite constant. The relation of the body weight to that of the enumerated genital organs was as 1:1200, i.e., the uterus and the ovaries weighed in milligrams somewhat less than the gram weight of the animal.

A few examples may elucidate:

Weight of guinea pig	:	Weight of uterus and ovaries
290 gm.	:	224 mg.
300 gm.	:	238 mg.
240 gm.	:	213 mg.
250 gm.	:	212 mg.

These investigations were conducted during all the four seasons of the year and it was found that genital growth, even in the virginal apparently still sexually unripe animals, is influenced by seasonal variations. This was particularly noted during the months of June and July, when the genitalia evinced hyperemia, succulency, and an increase in the thickness of the uterine wall. During these months the weight relationship of 1:1200 was no longer retained, because the uterus and the ovaries gained in weight. The latter weighed in mg. more than the corresponding gm. weight of the animal, the proportion has changed to about 1:900, as shown by the following figures:

Animal	Month	Weight	Weight of uterus and ovaries
No. 7	6-16-22	280 gm.	300 mg.
No. 8	7-17-22	280 gm.	464 mg.
No. 82	7-22-22	350 gm.	368 mg.

A second stimulating period is found at the beginning of the winter, during the month of November. At this time we have found the following proportions:

Animal	Weight	Weight of uterus and ovaries
No. 88	220 gm.	290 mg.
No. 21	210 gm.	230 mg.

The microscopic examinations of the ovaries showed that corpora lutea may form also in virgin guinea pigs. These animals were of an average age of six months. Very striking was the fact that the ovary presented a different appearance at different seasons. During the winter months the ovaries contained many cystic follicles, while during the summer the stroma was more compact. But there were many exceptions, so that we must be careful in the interpretation of these findings. If we should lay too much stress upon the conditions

just described then we may easily arrive at erroneous conclusions. For example, if the experiments are begun in April or in May and the injections of the trial preparation are continued up to June, most of the sectioned animals will show an hyperemia and an hyperplasia of the uteri. The logical conclusion would be that the preparation experimented with, has exercised a specific influence upon uterine growth; while in reality, the climatic condition constituted the active agent.

After having found an objective method in the weight estimation of the genitalia, and in the relation of their weight to that of the body, we have set for ourselves this problem: Is ovarian extract capable of stimulating uterine growth?

As Zondek has shown in his earlier investigations that the biologic reaction to organic extracts depends upon the nature of their production, particularly upon the method in which their albumin constituents are separated, we have undertaken to test the efficiency of different ovarian extracts. For this purpose the ovaglandols and the ovarian optons were selected. The former are chemically de-albuminized substances, prepared by the Grenzach laboratories; the latter are according to Abderhalden, produced by means of tryptic fermentation. Animal No. 81 received 15 c.c. of ovaglandol, on July 28, 1922, and besides a slight congestion of the uterine horns, showed no evidences of hyperplasia, the weight relationship stood 280 gm. : 280 mg. Animal No. 11, experimented upon in the winter, did show a marked reaction; the weight proportions were 210 gm. : 315 mg. These tests showed the inconstancy of this preparation, and that we possess no means, as was shown in previous experiments, of guaranteeing their uniformity of action. The results with the tryptically prepared ovarian optons, were altogether *nil*, the weight proportion was 280 gm. : 218 mg. The conclusion is, *that only with chemically prepared ovarian extracts, and not with those obtained through tryptic fermentation, may results be obtained from time to time.* The results which Aschner obtained with ovarian extract we could not verify. Even with the most active preparations, which will be considered later on, we could never get such intense reaction, as Aschner described and sketched. We are inclined to believe that some unknown source of error has crept into Aschner's experiments. No results were gotten with corpus luteum or with placental extract. As placental extract, we have used the placenta opton (hydrolytic preparation), with which Puppel[25] reported hyperplastic results. Puppel's investigation will be subjected to a critical analysis further on.

How do other organic extracts act? The tests with a chemically prepared testicular extract (testiglandol) showed a distinct result. After an injection of 20 c.c., in the course of two months the weight

proportion was 230 gm. : 309 mg. The uterus was thickened, the mucosa hypertrophic, with a pronounced hyperemia.

Still more striking were the results with pineal extracts on animal No. 22. With a body weight of 440 gm. we reached a genital weight of 896 mg., so that the proportion amounted to 1:500. The uterine horns were violet red and thick; microscopically a marked hyperplasia was noted of the muscularis, and particularly of the mucosa, which showed a rich glandular proliferation. The ovary contained a corpus luteum. But these results also vary, and are inconstant. Animal No. 21 received the same quantity of epiglandol as animal No. 22, without showing any growth changes of its uterus. The weight proportion amounted to 310 gm. : 260 mg.

Just as ineffective was the action with hypophyseal extract. After injecting 20 c.c. of hypophysis-opton into animal No. 33, the weight ratio was 290 gm. : 172 mg. With extracts from the anterior lobe, (anteglandol) in animal No. 80, the weight relationship was 260 gm. : 212 mg. These facts were particularly brought out in order to emphasize the unreliability of endocrine extracts. We know from experimental investigations (Aschner) and from clinical experience, that a growth relationship does exist between the anterior pituitary and the genital organs. After hypophyseal extirpation the genitals remain infantile in type. Dystrophia adiposa genitalis is also often associated with hypogenitalism. The fact that injections of hypophyseal extracts fail to produce genital hyperplasia does not prove that our knowledge of the interrelationship between the gonads and the hypophysis is false, it merely shows that the extracts employed do not contain that active principle which the hypophysis secretes *in vivo*. In conclusion we also want to mention that thyroid extracts proved inert, while thymus extract gave once a very striking result, verified microscopically by an hyperplasia of the mucosa, with a glandular proliferation. The ovary showed a fresh corpus luteum.

A summary of these experiments shows that we can stimulate uterine growth to a moderate degree with the glandol preparations made from the ovary, the testicle, the epiphysis and the thymus; while extracts from the same glands, only differently derived (the opton groups) fail to produce hyperplastic changes in the genitalia. The opton preparation of the placenta, the hypophysis, (the whole gland and its anterior lobe alone), of the thyroid and of the other endocrines, also proved to be valueless as growth-promoting agents. This may lead to the conclusion that certain glands do stand in relationship to genital growth, but such a conclusion is, according to our opinion, scientifically unjustified; for (a), gland and gland extracts are by far not the same, and (b) the method of preparation, whether chemical, or tryptically fermentative, greatly modifies the experimental and the therapeutic results. We also wish to call particular attention to the

fact that we, in contrast to Puppel, obtained no results with placental opton. Puppel makes no definite mention of the time of the year during which his experiments were carried out, and relies upon his optical powers of observation in making his growth estimates and comparisons. Puppel experimented with rabbits, and if we were to admit that rabbits react differently than guinea pigs, then we would have to doubt the authoritativeness of all such investigations. Furthermore, if a growth-stimulating substance would act upon a rabbit's uterus and not upon that of a guinea pig, it would be impossible to draw conclusions bearing upon human physiology or physiologic pathology. Puppel obtained no results with ovarian opton—did not this strike him as rather unusual? The first evidences of the internal secretion of the ovary and its influence upon uterine growth recorded in the literature were based upon the fact that through the administration of ovarian extracts uterine hyperplasia was produced; and if he failed to stimulate uterine growth with ovarian opton, he should have known that some unfilled gap is still yawning between the known physiologic facts and his experiments. So that if Puppel got results with placental opton, and not with ovarian opton, it would imply that the placenta does promote uterine growth, while the ovary does not. It is not quite clear to us why he ascribes altogether to the placenta properties which influence genital growth in virgin animals; for this function, if at all possible, can only be exercised by the generative glands. Now, therefore, if Puppel could obtain no action with ovarian extracts, but with placental extract prepared under the same conditions, then the conclusion must follow that the preparations were faulty.

THE ACTION OF ALBUMINOID SUBSTANCES

If some gland extracts can stimulate the uterus to grow, while others remain inactive, then the supposition lies close at hand that we are dealing with a nonspecific general action. This supposition gained in certainty from clinical observations of Stickel and Zondek,[26] who noted reactions to glandular extracts that could not be explained on biologic grounds. For instance, if testicular extract can act as a hemostatic agent in uterine bleeding of oophorogenic origin, then we can no longer speak of endocrine function, but must acknowledge some unspecific influence. A good deal of confusion was brought into the realm of endocrinology through wanton conclusion based upon the results of only a few experiments. It is untenable to prepare an extract from a gland, inject this into an animal, ascertain a result, consider it as specific, and upon these few facts build an hypothesis about endocrine function and correlation. In this wise many conclusions were reached as to the effect of some extracts upon blood pressure, and the endocrines were subdivided into two groups, blood-raising and blood-depressing agents. We need not doubt, however,

that the effect upon blood pressure depends entirely upon chance products, particularly upon the albumin bodies. Only keen clinical observation, and exact scientific criticism may advance the knowledge of opotherapy. So long as a biologic effect, produced with a given gland extract, may be duplicated with a nonspecific substance which is closely allied to the particular extract, so long are we not justified in speaking of "specificity of function." It seemed to us as an essential part of our inquiry to test the function of albumin bodies, for there are palpable indications that the albumin split products which form in the gland extracts during the process of their production, are responsible for the observed and recorded growth phenomena. The previously described results obtained with de-albuminized gland extracts were also produced with fresh gland preparations whose albumin content was not separated.

The following investigation will show that protein injections are capable of stimulating growth and that the parenteral administrations of albumin bodies calls forth a general nonspecific heightened activity. After ten injections of sterilized milk (aolan), amounting to twelve c.c., a slight growth reaction was noted. Animal No. 27 showed a definite enlargement of its uterus, an hyperemia of the mucosa, and the weight proportion was 300 gm. : 322 mg. The other organs also showed evidences of hyperplasia. The spleen weighed 396 mg. in contrast to the normal weight of 363 mg. Still more striking were the results with larger doses of aolan. Animal No. 94 after receiving 15.5 c.c. showed a marked enlargement of its uterus, a weight ratio of 270 gm. : 381 mg. The spleen was also enlarged, weighing 450 mg. With injections of 20 c.c., the action was still more pronounced. The vagina and the uterus had a violet red color, strongly hyperemic, the uterine horns were thickened, musculature and mucosa hypertrophic and the weight proportions, (animal 28) were 260 gm. : 529 mg. The enlargement of the spleen in this case was extraordinary, reaching 960 mg., which is almost three times that of the normal. The adrenals were also enlarged, and weighed from 115 to 140 mg. against 84 to 94 mg. normally. Whether we are dealing in this case with a general growth stimulation, due to the large quantity of aolan and its rich albumin content can only be surmised, as the number of tests in this investigation is insufficient. It is noteworthy that no result was obtained with caseosan, the uterus did not enlarge at all, and the weight ratio was 295 gm. : 286 mg. The casein is therefore not the active principle, but we must ascribe the growth promoting properties to other protein bodies in the milk, such as albumin and globulin, or other albumin split products. *The main fact established by these experiments is that the growth activity may be promoted through parenteral administration of albuminoid sub-*

stances with as much success as with the proclaimed specific ovarian extracts.

THE ACTION OF THE BIOGENIC AMINO BODIES

The organic extracts usually employed are albumin free, hence it must be assumed that the growth manifestations consequent upon their use must be due to the finely split albumin products which can no longer be detected with the biuret test. To clear this doubt, we carried out a series of experiments with biogenic amido bodies, particularly with those pertinent to our subject. Gugenheim[27] in his excellent monograph, gave a review of our present day knowledge of proteogenic amino bodies. It seems to us that the manifold occurrence of these substances in most biologic processes, and their partly specific action, has not up till now been sufficiently appreciated. The formation of biogenous amino bodies in the higher plants and animals takes place through intracellular fermentative changes, and also through bacterial decomposition of nitrogenous matter (putrefaction). Inasmuch as the biogenic amino bodies of higher animals and plants are not formed synthetically, they must form hydrolytically, or through a methylizing process of amino acids. In cases of putrefaction as a result of bacterial decomposition this formation takes place through a decarboxylizing of the amino acids. In order to evaluate the significance of these substances in biology, it may be noted that the hydrolytic breaking up of the nucleonic acids leads to purin and pyramidin bases, that the phosphatides split up cholin, and that the adrenal secretion, the adrenalin, belongs to the biogenous amino group.

Our tests with cholin lead us to the following conclusions: We know that cholin is present in all proteins of plant or animal derivation, it is therefore also contained in all organic extracts. We know that many effects, which were formerly considered as specific, like the lowering of blood pressure, are now known to be due merely to the presence of cholin in the organic extracts. But the effect of cholin upon uterine growth is negligible.

THE GUANIDIN COMPOUNDS

The guanidin compounds were recently studied very assiduously, and we also experimented with them. Guanidin is present abundantly in nature, either in a free state or in combination with its derivatives, the N homologues, which in the form of methylguanidin, creatin and arginin, play an essential rôle. Kossel called our attention to the directing rôle which arginin plays in proteid metabolism. The analysis of Kossel, Kutscher and Orgelmeister showed that arginin is present in almost all animal proteins: in the blood 2 per cent, in fibrin 3 per cent, muscle tissue about 4.7 per cent, kidney 4.2 per cent, heart 5.8 per cent, and liver 2.5 per cent. The ubiquity of this amino-

acid made us think that it may also be of importance in our investigation, but the experiments rendered a negative result. After twenty injections, amounting in all to one gm. of arginin nitrate, into animal No. 3, no growth increase of the uterus resulted. The weight proportion was 295 gm. : 210 mg. Neither did any of the other glands present evidences of growth increase.

Guanidin itself also proved to be functionless. After twenty injections, equal to 0.004 gm., the uterus remained thin and pale. The weight ratio was 295 gm. : 196 mg. The pharmacologic action of guanidin is to be conceived, according to Fuhner[28] as that of a monovalent guanidinium ion, which is analogous, physiologically, chemically and pharmacologically, to the natrium ions. Just as the potassium salts, so do the guanidin salts stimulate the functional activity of the striated muscles (Gugenheim). Uterine growth is not influenced by guanidin.

THE IMIDAZOL COMPOUNDS

The imidazol compounds seemed to us to be of special biologic interest, since they are capable of calling forth biologic actions even in small doses. This is particularly the case with B-imidazolylethylamin, and histamin. This is derived from histidin through the action of microorganisms. Fungi as well as bacteria possess the property of decarboxylizing histidin and form histamin. We know at present about thirty different varieties of bacteria which are endowed with this property. It is therefore not surprising to find histamin in so many products of decomposition. We may mention that Barger and Dale[29] and Kutscher proved that histamin is one of the active principles of ergot, and that it may be found in the intestinal wall, in the feces, in the urine, and in all products of putrefaction. The pharmacologic tests of these amino bases rendered characteristic effects upon the involuntary or smooth muscle fibers of the vegetative organs. According to the quantity administered, there will follow either a rhythmical enlargement, with increasing tonicity, or a steady maximal tone. In addition to this, histamin also exercises a high autonomic stimulation. B-imidazolylethylamin is active in the most minimal doses. With a solution of 1:500 millions contractions took place in the isolated uterus and intestine of a guinea pig. Histamin lowers blood pressure, increases pancreatic secretion, and contracts the bronchi. It is quite interesting to note that the toxicity of histamin varies with different animal species. Sieburg[30] showed that a frog weighing 30 gm. will show no toxic effects from injections of 20 mg. of histamin, while according to Leschke[31] a rabbit can only stand 12 mg. per kg. of body weight, and a guinea pig only 3.8 mg. We have found that the maximum dose for white mice, of an average weight of 30 gm., is 1.5 mg.; or 50 mg. when figured in kg. of body weight. The mouse

can therefore tolerate four times as much as the rabbit, and fifteen times as much as the guinea pig. In the human, even smaller doses of histamin than those used in the experiments proved to be toxic.

In order to study the effect of histamin, one of us injected himself subcutaneously with 0.4 mg., which is only $\frac{1}{10}$ of the guinea pig dose, and hardly $\frac{1}{100}$ of the dose for a mouse (calculated upon the body weight in kg). The effect was distinctly toxic, characterized by headache, dizziness, a feeling of anxiety and increase in the pulse rate. These symptoms lasted for about three hours. Further tests showed that subcutaneous injections of 0.2 mg. are well tolerated by human beings, while 0.3 mg. call forth the above described complaints. Intravenous injections of 0.02 mg. can unhesitatingly be tolerated by an adult human, while 0.03 cause headaches, etc. We shall take up the study of histamin somewhat more closely, for we believe that the amin base is of great importance for biologic processes and that it also plays no irrelevant part in human metabolism.

The fact that minimal doses of histamin call forth in the human marked reactions, with its concomitant toxic phenomena, and that these can be noted with the slightest increase in dosage, shows that even insignificant changes in the breaking up of the imidazol series may cause grave disturbances. The variance in the toxicity of the histamin dose in different animal species becomes evident when we calculate the dose of maximum tolerance upon the basis of body weight in kilograms. We obtain the maximum dose of histamin per kilogram of body weight as follows:

Frog	650 mg.
Mouse	50 mg.
Rabbit	12 mg.
Guinea pig	3.8 mg.
Human	0.4 mg.

If we increase the maximum dose in the human to 0.1 mg. per kg. of body weight, then the tolerance multiple in the guinea pig would rise to 400, 1200 in the rabbit, 5000 in the mouse and to 6500 in the frog. If we calculate the dosage upon the animal as a whole, then we find that a mouse weighing 30 gm. can stand five times as much histamin as an adult human being.

In previous experiments Zondek has shown that the hemostatic properties of some organic extracts (glandol preparations) are due to the contained proteogenic amino bodies. It can be proved that many endocrine extracts contain substances which cause contraction of the smooth muscles of the vegetative organs. Similar contractile powers are shown by extracts derived from liver tissue. If a process of albumin decomposition is undertaken, i.e., if we permit the liver tissue to undergo putrefaction then we will find in it muscle contracting sub-

stances in a high concentration. It is quite certain that these contraction producing substances are identical with those present in histamin, which are also the result of protein decomposition. It is also interesting to note that in the growth promoting substances, histamin is also an essential constituent. Histamin injections into guinea pigs cause with fair regularity an enlargement of the uterus, an increase in its thickness, and hyperemia. The effect was proportionate to the dose. After five injections, representing 3 mg. of histamin, the weight proportion was 275 gm. : 380 mg. After eighteen injections, amounting to 4 mg. of histamin, the weight relationship was 370 gm. : 369 mg. Histamin is therefore capable of increasing genital growth in infantile animals. The amount of histamin required for this purpose is quite large, 3 to 4 mg., for the guinea pig, which, as already stated, tolerates more histamin, or is far less sensitive to it, than the human being. The growth promoting function of histamin might possibly be ascribed to the continued contractions which it calls forth in the uterine muscle, in other words, to a work hypertrophy. Such a conclusion would be erroneous, for the experiments with amino bodies, which have a definite and specific contractile effect upon the uterus, failed to yield growth promoting results; histamin is therefore a growth stimulating specific.

PHENYLALKYL AND PHENYLALKANOLAMIN

From this group those amino bodies were tested whose biologic effect upon uterine contractions could be proved. These amino bodies contain a phenyl residue, by virtue of which the chemical as well as the pharmacologic properties of the aliphatic alkyls and alkanolamins are considerably changed. The naturally occurring fatty aromatic amino bodies originate presumably from proteins; this fact was long ago established with certainty for phenylethylamin and oxyphenylethylamin. For the other representatives of this group, like adrenalin, the protein relationship has as yet not been proved. We have tested tyramin (paroxyphenylethylamin) and the decarboxylizing product of tyrosin. The tyrosin belongs to the amino acids which are very quickly given off from protein. When casein and trypsin are digested *in vitro* there follows a deposit of tyrosin crystals on the walls of the container. Tyrosin is also found in human urine during metabolic disturbances, such as diabetic coma, phosphorus poisoning and prolonged anesthesias. Injections of tyrosin (eighteen injections aggregating 1.8 gm.) proved valueless in promoting uterine growth. The weight ratio corresponded to 300 gm. : 280 mg. Through a decarboxylizing process of tyrosin, tyramin is obtained; it is also present in ergot (Barger), and it may form during the process of digestion as a result of putrefaction. But, as tyramin undergoes a rapid change in the mammalian organism, its presence must be of a temporary nature only. The biologic effects

of tyramin have been carefully studied. We know that it raises the blood pressure, that it relieves bronchial spasms, and that it acts as a specific in stimulating the peripheral fibers of the sympathetic. By virtue of its specificity tyramin is capable of causing uterine and intestinal contractions, but in spite of this contractile power it is unable to promote uterine growth. After 20 injections of tyramin, amounting to 0.04 gm., into animal No. 30, we could not establish an increase in the size of the uterus. The weight ratio was 220 gm. : 186 mg.

Tyramin and histamin, which are contained in ergot, were recently employed as substitutes for the latter. It is claimed that tyramin is free from the toxic effects manifested by histamin, such as lowering of blood pressure, and is as efficient an oxytocic as is histamin. A mixture of both these substances (tenosin-Bayer) was shown by Zondek to be the best substitute for ergot. We have also tested out the effect of tenosin upon uterine growth, and have found that after injections amounting to 20 c.c., a very pronounced increase in the size of the uterus was noted, so that the weight proportion equalled 370 gm. : 630 mg. It is therefore certain that histamin possesses characteristic growth-promoting properties.

Adrenalin, the recognized active principle of the suprarenal gland, belongs to the same group. Our knowledge concerning adrenal function has advanced much further than that pertaining to the other endocrines, on account of our ability to produce adrenalin synthetically. In spite of this advantage we are still uncertain as to the biologic production of adrenalin within the organism; although it may be assumed that the rudiments of adrenalin must be looked for in one of the protein building stones (Bausteine), perhaps in tyrosin. The biologic functions of adrenalin on the other hand are definitely established, and we shall therefore consider only some of them. We know that minute doses of adrenalin stimulate the sympathetic and thus impart to the organs so innervated a sympathetic tone. Adrenalin contracts the peripheral blood vessels, thereby increasing the heart function, and raising the blood pressure. The pulmonary blood vessels remain uninfluenced by adrenalin, or they are not sympathetically innervated, in fact they undergo a slight dilatation. The effect of adrenalin on the uterus is expressed through a stimulation of the hypogastric nerves (Cushny). It is also interesting to note that the effect of adrenalin upon the uterus varies with the species, and also with the physiologic state of the uterus, whether gravid or not, in the same species. We must hence accept the fact that gravidity changes the nervous irritability of the uterus. Adrenalin causes uterine contraction in the rabbit, dog and ape; while in the cat, the mouse, and the guinea pig it causes uterine relaxation. The uterus of the virgin cat relaxes, and the gravid one contracts. Our experiments have

shown that 0.4 mg. of adrenalin, divided into nineteen injections were without any result, the uterus remained narrow and pale, the blood vessels partly filled; the weight proportion was 280 gm. : 220 mg. When the dose was increased to 2.6 mg. (divided into eighteen injections) in animal No. 99, a perceptible effect was noted, so that the weight ratio was 340 gm. : 620 mg. Notwithstanding the fact that small doses of adrenalin cause in the guinea pig a uterine relaxation, large doses are capable of promoting uterine growth. Whether this growth phenomenon is procured through the stimulation of the sympathetic cannot for the present be decided, since we do not as yet know what the sympathetic stimulation in the guinea pig is capable of rendering.

In conclusion we may also mention that the experiment with amino-valerianic-acids, alanin, aspargin and acetic-acid-ester, gave no result in reference to promoting uterine growth.

RÉSUMÉ

Briefly our results are as follows: By means of ovarian extracts (ovaglandols) we have frequently succeeded in bringing about an increase in the size of the uterus; with optons the result was negative. This is an additional proof of Zondek's conception that *the biologic action of organic extracts varies with the method and manner of their preparation.* We have obtained identical results with extracts of other glands (testicular and pineal) as with those of the ovary. Extracts of the anterior lobe of the pituitary yielded no results; although physiologically, a growth relationship between this portion of the hypophysis and the generative organs does exist. Genital growth may be stimulated by the administration of nonspecific biogenic amino bodies, which are the result of protein decomposition, as well as by the so-termed specific extracts. And since amino bodies may form in every organic extract, we must conclude that the slight increase in the size of the uterus noted after the administration of ovarian extract is not specific in nature. We cannot obtain a true endocrine effect with ovarian extract, for in the process of its preparation the active principle is destroyed.

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1125 Madison Avenue.

A POSSIBLE FACTOR CONTROLLING THE WEIGHT OF THE NEWBORN. RELATIONSHIP OF THE AREA OF THE PLACENTA TO THE BIRTH WEIGHT OF THE CHILD BASED ON OBSERVATIONS IN ONE HUNDRED CASES*

By Rae Thornton LaVake, M.D., Minneapolis, Minn.

(*Assistant Professor of Obstetrics and Gynecology, University of Minnesota*)

THE problem of birth weight, in cases of borderline measurements in the mother, has long been a subject of practical importance for all obstetricians. No doubt we have all tried to limit birth weight in such cases by various diets, the best known of which is that advocated by Prochownik. My results in such attempts have been signal failures. Women, under practically identical conditions of individual size, size of husbands and diet, have given birth to babies of widely different birth weight; large women, who could not be persuaded to control the extent of their diet, have had very small children; and little women, with small husbands and careful in their diet, have had children above the average birth weight. This experience has obtained in the practice of many obstetricians.

In regard to birth weight and diet, researches to date seem to show that, although overeating may add to the birth weight of a child, biologic facts do not show that restriction of diet below normal will noticeably influence or retard the growth of the fetus. Such restriction is only a detriment to the mother because the placenta will furnish necessary substances for the development of the fetus as long as they are available in the mother. If not available in excess of the needs of the mother, the fetus will develop at the expense of the mother.

In cases where large women had small babies and small women

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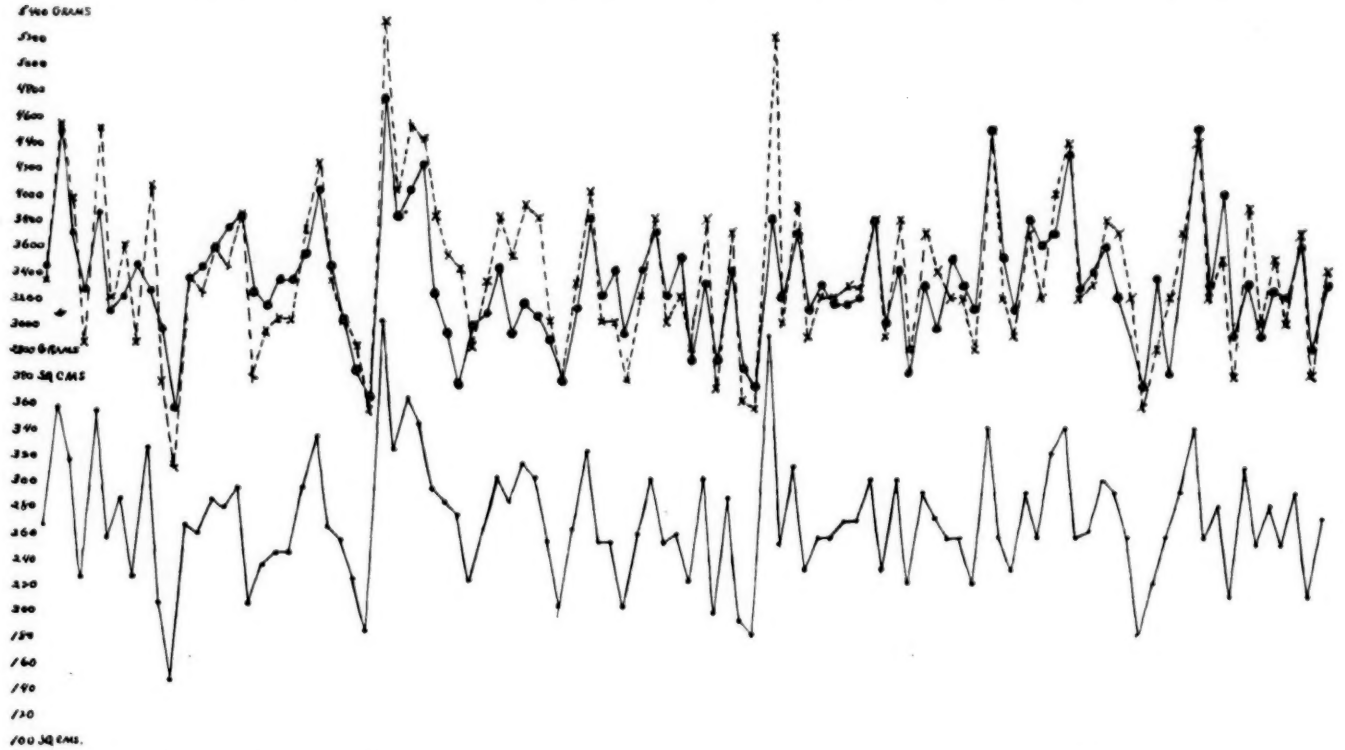
Chart giving re'ationship of the area of the placenta to the birth weight of the child in one hundred cases.



Dotted line connects points giving estimated weight in grams of newborn figured from area of placenta in sq. cms. Upper black line connects points giving acutal weight of newborn in grams. Lower black line connects points giving area of placenta in sq. cms.

had large babies, the concomitant feature which has nearly always attracted my attention has been the size of the placenta, large with large babies and small with small babies. The accompanying chart shows the relationship of the area of the placenta, in square centimeters, to the birth weight, in grams, in the last hundred cases coming under observation. I believe there is a parallel relationship. It is suggestive though possibly fortuitous in such a small series of cases.

The question will naturally suggest itself whether the weight of the placenta or a combination of the weight and the area parallels the birth weight more closely. Both relationships were tried but the parallel was not so marked, possibly because equal conditions of retained blood in the placentae could not be controlled.

The area of the placenta was arrived at in the following manner: Having determined that the placenta was intact, it was laid, uterine surface down on a hard surface, and flattened out by approximately a given pressure. A heavy, nonelastic thread was then laid around the edge, following the sinuosities, and then drawn straight and measured in centimeters. Taking this measurement as the circumference, the area was figured. The accuracy of the study was curtailed by the great likelihood of error in measuring the circumference. Several measurements of the same placenta varied frequently by from three to five centimeters which, if not corrected by an average of several readings, would cause a difference of as much as five hundred grams in estimating the birth weight. Even the average readings could only be viewed as rough approximations. Then again, no accurate determination was made of the area destroyed by infarctions, except to note that, in each instance where the actual birth weight fell below the birth weight estimated from the area of the placenta, in that placenta infarction was marked. In the first thirty cases the average quotient obtained by dividing the actual birth weight, in grams, by the area of the placenta, in square centimeters, was 12.5. In the next seventy cases this figure was used to estimate the probable birth weight of the child, after obtaining the area of the placenta. Even with this inaccurate quotient, 12.5, because taken from such a small number of cases and under the handicap of marked inaccuracies in determining the actual functioning area of the placenta, represented by the noninfarcted area of the placenta, it was interesting to note how closely one could estimate the birth weight of the baby in the great majority of cases.

If this parallel between the area of the placenta and the birth weight is not fortuitous, the deduction possibly to be drawn is that the impregnated ovum having the most proteolytic power "digs in" the deepest in the uterus with the final formation of the largest pla-

centa, thereby assuring the greatest possible access to the food supply, resulting, other factors being equal, in the largest birth weight. This deduction, if warranted, would have only suggestive significance because I believe the preponderance of biologic evidence points to the fact that the potential size of the child at birth resides in the impregnated ovum from the start. This potential might very likely parallel the proteolytic energy of the ovum, thus accounting for the size of the placental formation, which is believed by some to be the result of protective mechanism on the part of the maternal structure to limit further proteolysis. Again, if this deduction can be drawn, the logical corollary would be that impregnated ova of diminishing degrees of proteolytic power would likely be swept nearer and nearer to the internal os before being able to "dig in" with resultant lateral, partial and central placenta previa formations. I have no data outside of cases too few to be of any significance, which would tend to substantiate the usual presence of small placentae in cases of placenta previa delivered at term.

Another logical corollary would be that, even with normal tubes, ectopic pregnancy may be accounted for by the high proteolytic power of the developing ovum which causes it to "dig in" before reaching the uterine cavity. This would account for the frequency of later ectopic pregnancy in the opposite tube, left in at the time of operative interference in the first ectopic pregnancy because of the apparent normality of this tube.

This chart, with possible deductions therefrom, may be of practical value only as it may add evidence in corroboration of the experimental and clinical futility of the attempt to produce subnormal birth weight by dietary regime, which is not one of the primary factors in control of birth weight. In directing the diet to subserve the strength and well-being of the mother we subserve the best interests of both the child and mother. Necessary obstetrical maneuvers and operations with a strong, healthy mother offer greater chances of success than any restriction of diet below the adequate needs of the mother in the effort to diminish the size and weight of the child at birth and thus bring about a more easy labor.

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DONALDSON BUILDING.

THE INCIDENCE AND SIGNIFICANCE OF UROGENITAL SYMPTOMS IN GYNECOLOGIC PATIENTS*

By Walter T. Dannreuther, M.D., F.A.C.S., New York City

(Associate Professor of Gynecology, New York Post-Graduate Medical School and Hospital; Attending Gynecologist, St. Elizabeth's Hospital; Consulting Female Cystoscopist, Lutheran Hospital.)

AFTER four years in general practice, and another four of gynecology, I acquired a working knowledge of cystoscopy in 1914. During these eight years women complaining of symptoms referable to the urinary tract were treated for "cystitis" without any real study of the urinary pathology, unless the severity of symptoms demanded consultation with a urologist. Since 1914, however, such patients have received the benefit of a cystoscopic examination, supplemented by such further urologic investigation as was deemed necessary. Retrospection now convinces me that: (1) many gynecologic patients manifest symptoms referable to the urinary tract; (2) in women, there is such a close relationship between the pelvic and urinary organs, that symptoms originating in one group are frequently referred to the other; (3) no gynecologist is equipped for the practice of his specialty until he becomes proficient in cystoscopy; (4) it is not necessary that the gynecologist become a urologist, but he must be qualified to recognize lesions of the urinary tract promptly and treat them intelligently; and (5) these facts are not appreciated by all gynecologists.

My own early sins of omission and the observations made during the last ten years have so inculcated the truth of these aphorisms that herewith I venture to submit a review of 600 consecutive private case records. No dispensary or hospital ward records have been included, because histories taken by different individuals lack uniformity, and patients coming to the ward service are usually selected cases and candidates for some definite gynecologic operative procedure. No obstetric cases are included in this presentation.

While I have no inclination to compile a series of statistical tables, which, as has well been said, "may be made to prove anything, even the truth," yet the occurrence of urinary diseases in gynecological practice and the relative significance of the several symptoms discovered in the analyses of these histories must necessarily be gauged to a considerable extent by their mathematical frequency.

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A study of the case records reveals:

Patients having no urinary symptoms	481
Patients having some pathologic condition of the urinary tract, or symptoms referable to it	119
Total	600

It is therefore evident that 20 per cent of patients consulting the gynecologist require cystoscopic examination to establish a diagnosis. Of the 119 patients constituting the basis of this investigation, 53 had urinary symptoms only, while 66 had both urinary and pelvic symptoms. But the fallacy of relying upon symptomatology for diagnosis is well illustrated by the causative factors discovered:

Patients having lesions of the urinary tract	51
Patients having lesions of both the urinary and pelvic organs	44
Patients having lesions of the pelvic organs only	14
Patients having urinary symptoms due to remote causes	10
Total	119

In the 95 patients having actual disease of the urinary tract, either alone or associated with some pelvic lesion, the following pathologic conditions were present:

Pyelitis		18
Acute		
Suppurative	7	
Hemorrhagic	1	
Chronic	10	
Trigonitis		
Cystocele		15
With irritation of bladder	11	
With trigonitis		
Urethral carunele		10
Uncomplicated	4	
With chronic pyelitis	2	
With cystocele and trigonitis	1	
With trigonitis and urethritis	1	
With supernumerary ureter		
With supernumerary urethra	1	
Urethritis		8
Acute cystitis		6
Prolapsed kidney		6
Uncomplicated	3	
With chronic pyelitis	2	
With hydronephrosis	1	
Renal calculus		3
Ulcerative cystitis		3
Ureteral stricture with chronic pyelitis		2
Periurethral abscess		2
Renal tuberculosis		2
Bilateral polycystic kidney		1
Pyonephrosis		1
Relaxed vesical sphincter		1
Papilloma of bladder		1
Carcinoma of badder (secondary)		1
Total		95

A general survey of these cases discloses many facts of clinical importance, but before discussing the several diseases separately, I desire to call attention to the practical value of two easily utilized diagnostic

aids; catheterization of gynecologic patients, and the routine use of the indigo-carmine renal function test.

Catheterization of Gynecologic Patients.—An empty bladder is a prerequisite for satisfactory bimanual examination. To preclude contamination, a specimen of urine must be fresh, obtained by catheter, and drawn into a sterile receptacle. I have, therefore, adopted the practice of catheterizing all gynecologic patients on their first visit, collecting the specimen in a long sterile test tube, after the fashion of the urologist. This method not only insures complete emptying of the bladder before making the pelvic examination, but also affords an excellent opportunity to examine the urine "body," with reference to its physical properties. Turbidity, discoloration, and the flakes, filaments, and shreds suspended in the urine are detected by twirling the tube. The same urine is available for smears or cultures, should they be deemed necessary. There is often a decided difference between the appearance of a freshly catheterized specimen and one contaminated by passing the vulva, and brought in a bottle by the patient after the lapse of considerable time. The advantages of catheterization are obvious. Inspection of hundreds of catheterized specimens of urine from women warrants the following conclusions:

Discoloration of the urine is due to the presence of blood, bile, or some chemical agent.

Turbidity of a milky character, cleared by adding a few drops of acetic acid, is due to phosphaturia.

Turbidity of a milky character, not cleared by acetic acid, is due to bacteriuria.

Flocculent material that does not tend to settle to the bottom of the tube is mucus.

Flocculent material that becomes "ropy" on twirling of the tube, and tends to settle afterwards, is pus.

Visible small granular flakes, equally distributed throughout the urine "body" are often a manifestation of pyelitis.

Large flakes and shreds usually come from the bladder or urethra, and often denote a cystitis or urethritis.

Indigo-Carmine Renal Function Test.—Of all the renal function tests, this one is probably the most easily applied and consumes the least time. Although it does not represent the metabolic capabilities of the patient as accurately as the phenolsulphonephthalein, it quickly indicates any impairment of renal function or ureteral obstruction on one or both sides. I would strongly urge that the gynecologist carry it out in every patient with chronic appendicitis, cystic ovaries, and other diseases to which pain in the lower abdomen is so often ascribed, before subjecting the patient to operation, as its behavior may suggest the presence of some lesion in the kidney or ureter, which in reality is

producing the symptoms erroneously attributed to coexisting pelvic pathology. When the indigo-carmine is given intravenously, the technic is simple, elimination rapid, and the test reliable.

Pyelitis.—The most striking feature of this disease is the frequency with which it occurs in women. Adding the two cases of urethral caruncle, the two of prolapsed kidney, and the two of ureteral stricture, in which there was a coexisting pyelitis, to the 18 uncomplicated cases, makes a total of 24; 25 per cent of the whole number of the diseases of the urinary tract. Practically all of these, of course, showed a concomitant involvement of the bladder in the inflammatory process, so that although intravesical treatment would have failed to cure, a diagnosis of "cystitis" would not have been entirely wrong.

While many of these patients unquestionably acquired pyelitis as a lymphogenous or hematogenous infection, secondary to their constipated tendencies or focal infections, I have been impressed by the number of instances in which the onset in the under-nourished, anemic type of individual has followed sea bathing in the late summer months. In such cases, when the patient was at a resort, the local physician usually made a correct diagnosis during the acute stage, but limited his treatment to medical measures. Several of the patients with chronic pyelitis had been treated for variable periods of time by other physicians with indifferent success. All required irrigations of the renal pelvis through a ureteral catheter for cure. The acute cases were all suppurative but one, which was hemorrhagic in character.

Fourteen patients had previously been treated unsuccessfully by other physicians for periods of from three weeks to 23 years; 1 for three weeks; 2 for 4 months; 3 for 6 months; 5 for 1 year; 1 for 2 years; 1 for 10 years; and 1 for 23 years. The patient who was treated for 23 years had many nervous symptoms and had been in the hands of another gynecologist for a long time. Apparently in desperation he had cut down on the right kidney because of severe lumbar pain seven years before I saw her, without a preliminary cystoscopic examination. This woman was completely cured in six months by instillations of silver nitrate into the renal pelvis.

The urine from patients with pyelitis without exception showed alterations in its macroscopic appearance. Those with acute inflammation had a pronounced pyuria or bacteriuria, while those with chronic involvements showed small granular flakes or small shreds in the catheterized specimen. Four of the acute cases also had hematuria, in three of which the pyogenic features predominated and the bleeding occurred intermittently. In the other case, the hematuria represented a real hemorrhagic pyelitis.

Colon bacilli were found in the urine in 16 cases, staphylococci in 7, and streptococci in one case.

The elimination of indigo-carmine was delayed beyond 6 minutes from the affected side or sides in 18 cases, but never more than 12 minutes.

In each case of pyelitis there was an inflammatory involvement of the bladder, so that a certain degree of cystitis may be accepted as a concomitant of the disease, the acuity of the bladder inflammation often corresponding to the intensity of the pyelitis. The bladder capacity was markedly diminished in two cases of suppurative pyelitis, to 5 ounces and 3 ounces respectively, and in both instances there was a pronounced cystitis.

Of the 24 patients, 16 had urinary symptoms alone, and eight urinary and pelvic symptoms combined. Only two had an associated pathologic condition of the pelvic organs to which some of the symptoms might fairly be attributed (retroversion of the uterus in both instances). The menopause was incidental in two other cases. The most common symptom was frequency of urination; diurnal and nocturnal in 19 patients, and diurnal only in two others; three were entirely free from this annoyance. The next most constant symptom was lumbar pain or discomfort. This occurred in 18 patients, while hypochondriac distress on the affected side was mentioned only five times. When a woman talks about "backache," it is a good idea to make her indicate its exact location by putting her hand on it. This is certain to prevent the not infrequently made mistake of assuming that she refers to the sacral region, when she really means the lumbar, and a mobile retroverted uterus will not be unjustly accused of causing it. Inguinal pain was noted in three cases: in the two of ureteral stricture with chronic pyelitis and in one case of prolapsed kidney with pyelitis. Urgency of urination appeared, seven, suprapubic discomfort, seven, burning sensation on voiding, five, tenesmus, three, and urethral discomfort three times. Pyrexia was observed in all cases of acute pyelitis, but in none of the chronic cases.

Trigonitis.—This is defined by Dorland as "an inflammation or localized hyperemia of the trigone of the bladder," which actually implies a chronic cystitis. When preceded by acute cystitis, the primary inflammation usually involves the entire bladder wall. This subsides rapidly, and except in those cases in which resolution and recovery are complete, there remains a chronic inflammation, which is either restricted to or more pronounced in the region of the trigone. On the other hand, a large number of cases are insidious in onset and chronic from the beginning. A certain degree of trigonitis invariably accompanies chronic pyelitis, so that the number of patients having this latter condition must be added to those with trigonitis alone. If all these are grouped with all the cases having acute inflammations, it is quite evident that the diagnosis of "cystitis" will be at least partially correct in about 50 per cent of gynecologic patients having urinary symptoms. The term "trigonitis," as generally used, refers to a chronic cystitis, limited chiefly to the region of the trigone, and usually seen as a trigonitis

pseudomembranosa or cystitis cystica. In chronic ulcerative and hemorrhagic cystitis the pathologic processes extend so far beyond the confines of the trigone that they cannot properly be included in this category.

The catheterized urine from every one of the cases of uncomplicated trigonitis showed either turbidity or comparatively large flakes and shreds. Cultures developed colon bacilli in nine cases, staphylococci in three, and micrococci catarrhalis in one case. In two instances no microorganisms could be recovered: one in which the trigonitis was apparently due to extraneous causes (postoperative adherent anteversion of the uterus) causing extravesical pressure, and another in a patient coming for the relief of bladder symptoms after a nephrectomy for pyonephrosis by another surgeon. One patient had been treated for six months by a general practitioner, and was referred to me for "tuberculosis of the bladder." The doctor stated that on one occasion he had found tubercle bacilli in the urine. He had undoubtedly examined a voided specimen, contaminated by contact with the vulva, and mistaken the smegma bacillus for the tubercle bacillus. Such an error is unlikely if the bladder is catheterized. In no case was there any reduction of the normal bladder capacity.

Indigo-carmine was eliminated from both ureters in less than six minutes in all cases.

Both urinary and pelvic symptoms were present in seven of the 15 patients, and six of these had coincident pelvic disease, the other had an intestinal stasis causing pelvic symptoms. Diurnal frequency occurred in 12 patients, and nine of these had nocturnal annoyance too. One patient had nocturia without any during the day. Two had urgency and tenesmus without any frequency whatever. The patient who had had a nephrectomy complained of dull discomfort in the lumbar and hypochondriac regions on the opposite side, probably due to compensatory hyperactivity of the remaining kidney. Only one other patient had hypochondriac pain, and this was due to cholecystitis. Six patients had urgency, 3 tenesmus, 3 suprapubic discomfort, and 1 impaired bladder control. No patient complained of urethral discomfort, burning on voiding, or inguinal pain, and none had any elevation of temperature.

Cystocele.—Many patients with cystocele are free from urinary symptoms. In these cases the prolapse of the bladder is not very extensive or the patient comes under observation early. But others do have annoyances which can justly be referred to the bladder. In these cases cystoscopy is of material aid, for should a trigonitis be present, it is only fair to warn the patient that the operative correction of the cystocele is but the first step in her treatment and subsequent intravesical instillations will be necessary. Otherwise the persistence of symptoms after operation will be disappointing. When the cystocele is pronounced

there is always some distortion of the bladder which gives rise to at least a capillary congestion. This, together with the tendency to urinary stasis, renders the bladder particularly susceptible to microbic invasion. The fifteen cases considered as representing purely a pathologic condition of the urinary tract include only the ones attended by urinary symptoms.

The physical properties of the urine are not affected by the extent of the cystocele, but are entirely dependent upon the intravesical inflammation and infection. The urine was clear in all the patients except the four in whom cystoscopy showed a definite trigonitis. In these there was turbidity, with large flakes or shreds, and colon bacilli were found in each one. The cystocele was accompanied by complete uterine prolapse in three cases, there being about one ounce of residual urine in each instance. One of these patients apparently had a diminished bladder capacity, as she could not tolerate more than three ounces of fluid, but this was probably due to extreme irritability of the mucosa rather than to actual contraction of the bladder wall.

All but one of the 15 patients had both urinary and pelvic symptoms and all had some coexisting pelvic lesion, while one was also syphilitic and another had a definite hyperthyroidism. The patient with urinary symptoms only had a huge cystocele, but only a moderate perineal laceration with it. The most characteristic symptom in cases of cystocele seems to be that on lying down the patient experiences relief from all her other urinary symptoms, whatever they may be. Diurnal frequency occurred in 11 of the 15 cases, but only two complained of nocturnal annoyance. Another had nocturnal frequency only. Control was impaired in five patients, varying from occasional dribbling to involuntary voiding on coughing, sneezing, and exertion, and actual incontinence. In two of these the vesical sphincter was decidedly relaxed, and all but one (the syphilitic patient) were cured by a Kelly operation on the vesical neck and correction of the cystocele. Only four patients complained of urgency, and they were the four with trigonitis. All these women with cystocele were conscious of "something coming down."

Urethral Caruncle.—In view of the fact that in six of the ten cases of caruncle there was an additional pathologic condition of the urinary tract, it is obvious that removal of the caruncle would not always have sufficed to relieve the patient entirely.

One of the two cases associated with a urogenital anomaly was unique. This patient complained of sharp urethral pain and burning on urination, with some diurnal frequency probably due to circulatory hypertension. Examination disclosed a small, exquisitely sensitive excrescence on the vestibule, just below the normal external meatus. A probe, pushed through a tiny slit in its center, met with little resistance and traversed a path upward, backward, and to the right. Having

introduced a cystoscope into the bladder, the probe was seen to emerge through an aperture in the bladder wall, a little above and to the right of the right ureteric orifice. This patient had a second anomalous urethra, at the orifice of which was a caruncle. Removal of the latter effected a prompt cure of the patient's symptoms. The canal was later inspected through a small Kelly endoscope, and found to have a mucous membrane lining.

A caruncle does not produce any change in the character of the urine, so that alterations in its appearance are of course due to some other cause. Likewise, all symptoms other than urethral discomfort and burning are due either to some complicating factor or reflex irritation. Diurnal frequency, which occurred in nine of the ten cases, and urgency of urination may fairly be attributed to the latter. The patients having a concomitant pyelitis, trigonitis, or urethritis manifested the diversity of symptoms which these conditions are capable of producing.

Urethritis.—Of the eight cases of urethritis, seven were due to gonococcal infection and one to the micrococcus catarrhalis. Half the cases were acute when first seen, and the others chronic. In the acute stage the diagnosis was proved by urethral smears; in the chronic stage by smears and urethroscopy. The urine was turbid, containing large flakes and shreds, while the infection was active, and gradually cleared as the inflammation subsided. One patient with acute gonorrheal urethritis had a simultaneous perineal chancre, another an acute Bartholin abscess, and another an acute salpingitis. All eight had diurnal frequency, but only six had nocturnal annoyance. Burning on voiding occurred in six, urgency in six, urethral pain in two, and tenesmus in two cases.

Acute Cystitis.—A tentative diagnosis of acute cystitis can be made from the intensity of the symptoms, and cystoscopy or any other form of instrumentation is temporarily contraindicated. Acute cystitis, *per se*, can be differentiated from acute pyelitis, which may be accompanied by a cystitis, by the absence of fever. Fever was not observed in any case of infection limited to the bladder.

In every case there was a frank pyuria due to the colon bacillus. In many cases of acute colon bacillus infection of the bladder it is difficult to account for the migration of the microorganisms from the colon through the blood or lymph channels, and in several instances of this kind I have attributed the infection to the careless personal habits of some women. It does not require much imagination to conceive of a smear of colon bacilli being transmited from the anus to the vulva.

Diminution of the bladder capacity to five ounces was noted in three patients. This was only a transitory intolerance, the capacity increasing with alleviation of the inflammation.

The symptoms produced by the intravesical acute inflammation are so severe that the patient's attention is distracted from any other annoyances that she may have at the same time. For this reason, none of the

six patients mentioned anything but the urinary symptoms. While their nature does not differ from the symptoms arising from urinary disease, acute cystitis is characterized by the intensity of the symptoms. Not infrequently they are agonizing. All six patients had diurnal frequency, and all but one nocturnal frequency; five had burning on urination, four suprapubic pain, three urgency, three tenesmus, and one urethral pain. The absence of hematuria and pyrexia in all six cases is significant.

Prolapsed Kidney.—Not so many years ago, well within my recollection, all sorts of vague abdominal, pelvic, and nervous symptoms were ascribed to "prolapse of the kidney," if the kidney came down sufficiently on deep inspiration to permit of palpation. The number of women unnecessarily operated upon in the past for this condition had best be forgotten. As a rule, renal prolapse is simply an easily identified participant in a general visceroptosis. When a kidney prolapses as far as the true pelvis, however, there are two definite indications for radical and permanent corrective measures: Dietl's crises, produced by torsion of the pedicle, and damage to the renal histologic structures, caused by obstructed urinary drainage. The six cases classified as prolapsed kidney in this series complied with the above principles, the kidney having migrated to the pelvic region. The three that were uncomplicated required nephropexy for the relief of typical Dietl's crises, while the one with hydronephrosis had such extensive destruction of renal tissue that nephrectomy was necessary. Once the vicious circle of obstructed drainage, back pressure, urinary stasis, and infection becomes established, correction of the prolapse is imperative.

The character of the urine is of course influenced by the complicating factors, such as nephritis, pyelitis, and infection. Colon bacilli were found in the specimens from the 2 cases with pyelitis, and staphylococci from the one with hydronephrosis.

The elimination of indigo-carmine was delayed beyond the maximum normal time limit in all cases. No trace of color was seen coming from the hydronephrotic kidney, after twenty minutes observation.

Pelvic symptoms were present in addition to the urinary symptoms in four cases, being due to a large ovarian cyst, a large intraligamentary cyst, the menopause, and chronic intestinal stasis respectively. Typical Dietl's crises occurred in three patients. Increased frequency of urination was not a constant symptom, being noted in only three cases. Hypochondriac discomfort or pain was present in four, lumbar in three, and inguinal in one case. The inguinal pain was probably due to a large ovarian cyst on the same side, rather than to the renal prolapse.

Renal Calculus.—An elderly woman had been treated by another

physician for two years for "lumbago." Roentgenography disclosed two small calculi in the lower pole of the right kidney. Another middle-aged woman had had her gall bladder removed for the relief of pain in the right hypochondriac and lumbar regions, but the same symptoms persisted after operation. Again the x-ray revealed calculi in the right kidney. The third patient had been advised to have her left "cystic ovary" removed for the relief of pain in the right inguinal region which radiated to the groin, and requested me to verify the diagnosis and agree that operation was necessary. Since I could not determine any enlargement of the ovary, an indigo-carmine function test was done. No dye escaped from the ureter until 15 minutes had elapsed, and only traces appeared after that. A wax-tip ureteral catheter was arrested 11 cm. from the ureteric orifice, and the wax bulb showed deep scratches on its surface. Subsequent x-ray examination disclosed a large calculus in the left ureter. These cases well exemplify the desirability of utilizing a renal function test on the slightest suspicion of trouble in the urinary tract.

The urine from the first patient showed evidences of chronic interstitial nephritis. That from the other two was normal.

The elimination of indigo-carmine was delayed on both sides in the first patient, probably because of the nephritis rather than the calculi. In the second and third patients there was a decided interference with the ejection of the dye from the affected side.

All three patients had pain in the hypochondriac region, corresponding to the location of the calculi, and the two with stones in the kidney substance had lumbar pain as well. The patient with a stone in the ureter had pain along the crest of the ilium, which disappeared on lying down. All three had diurnal frequency without any at night.

Ulcerative Cystitis.—Syphilis and tuberculosis were excluded in the three cases placed in this category. Ulcerative cystitis seems to be characterized by a more or less general involvement of the bladder, irregularly distributed areas of small ulcerated spots, and an inflammatory reaction of the subacute type, with a corresponding severity of the accompanying symptoms.

The urine "body" contains large flakes and shreds, and epithelia from the middle and deep layers of the bladder wall can be found microscopically. Any of the more common pyogenic microorganisms may produce an ulcerative cystitis. In one of the three cases the bladder capacity was reduced to four ounces, and in another to five ounces.

Diurnal and nocturnal frequency were pronounced in all three cases. Urgency was intense in two, burning on voiding in one, tenesmus in one, and hematuria in one patient. In an elderly woman the bladder

control was distinctly impaired, but this could not be attributed entirely to the cystitis.

Ureteral Stricture.—For several years Hunner of Baltimore has insisted that stricture of the ureter occurs frequently in women. The most significant feature of the two cases encountered in this series is the fact that the strictures escaped detection and the patients suffered unnecessarily for a comparatively long time. In the first case the patient was subjected by another operator to a left oophorectomy and resection of the left tube two years before I saw her. As her symptoms persisted thereafter, she was referred to me by her family physician, and I made the mistake of operating upon her again, without doing an indigo-carmine function test first. At this time I removed a hydrosalpinx in the stump of the left tube, and the right ovary, which had become cystic. Only when I found that the symptoms still continued after this operation did I appreciate the necessity for a urologic investigation. The elimination of indigo-carmine was delayed on the left side, and the ejected stream was small and sluggish. Subsequent ureteral catheterization and pyelography demonstrated a narrow stricture of the left ureter, dilatation of which, together with a few irrigations of the renal pelvis, entirely cured the patient. It was this case which caused me to adopt the practice of doing a function test before all elective gynecologic operations. In the second case, the patient's physician had treated her for extreme nervousness and other symptoms for more than a year.

The urinary changes are those which are usually found in cases of chronic pyelitis, which nearly always follows a stricture of the ureter, if the latter has existed for any length of time.

The behavior of the indigo-carmine function test is often suggestive. Not only is the elimination delayed on the affected side, but the caliber of the stream is reduced, and the dye dribbles from the ureter instead of appearing in forcible spurts.

Both patients had diurnal and nocturnal frequency, and a discomfort along the crest of the ilium. Both also suffered from various nervous symptoms, which disappeared after a cure was effected. No other symptoms were present.

Periurethral Abscess.—This condition is undoubtedly a sequel of urethral infection, but both patients presented themselves with a well defined abscess already formed. One had previously ruptured into the urethra, and the other did so before the patient reached the hospital for operation. The urethral sinus closed promptly, however, in each instance, as soon as the abscess wall was excised, and the cavity healed by granulation. Subsequent topical applications soon cleared up the urethritis.

The urine in both cases contained pus, and the quantity excreted

from the urethra was so excessive that the patients complained of leucorrhea, although neither had a real vaginal discharge. Cultures from the abscess cavity showed colon bacilli in one case and staphylococci in the other. No gonococci were found in smears from the urethra, vagina, or cervix in either case.

The chief complaint of both patients was urethral pain. One had urgency, and the other burning on urination. These were the only symptoms except the supposed leucorrhea. Neither had any increased frequency of urination.

Renal Tuberculosis.—While only two cases of urogenital tuberculosis were encountered in this series of private patients, the incidence of this condition in hospitals and dispensary practice is considerably higher. The subject is one of such importance and of so many ramifications that the limitations of this paper permit but a brief allusion to the most salient points. (1) the patient's symptoms are usually referred to the bladder, seldom to the kidney, and differ little from those produced by other lesions of the urinary tract; (2) tuberculosis cystitis is invariably secondary to renal tuberculosis; (3) these patients particularly are apt to go from one physician to another without a correct diagnosis being made; (4) the tubercle bacilli are often extremely difficult to find in the urinary sediment; and (5) local treatment of the cystitis is useless until the offending kidney is removed.

Urogenital tuberculosis should be suspected in women when the bladder is intolerant of even bland fluids; when the capacity is reduced to four ounces or less; when cystitis fails to respond to the ordinary remedial measures after a reasonable length of time; when intravesical irrigations with silver nitrate aggravate the patient's symptoms; when there is more involvement of one lateral half of the trigone than the other; when there is a linear ulcer on the anterior wall or obstinate ulcers elsewhere; and when there is marked distortion of a ureteral orifice.

One of the two patients had been in the hands of other physicians for one year; the other for five years. The urine was fairly clear and highly acid in one, but was turbid in the other, probably because of mixed infection. In one case the tubercle bacilli were found easily; in the other they were discovered only after repeated search. The bladder was extremely intolerant in both cases.

No indigo-carmine was excreted from the diseased kidney within 20 minutes after intravenous injection in either instance. The ureter on the affected side in both cases was so involved that a No. 5 ureteral catheter could not be introduced.

Both patients had pronounced diurnal and nocturnal frequency, suprapubic discomfort, and afternoon pyrexia. One had urgency and tenesmus. The other had lumbar and hypochondriac pain, largely

due to perinephritic suppuration. Neither had hematuria. Both patients were cured by nephrectomy, followed by intravesical irrigations.

Miscellaneous.—The patient with bilateral polycystic kidneys is now thirty-eight years old, and has been under observation for seven years. During this period she has been successfully operated upon for complete prolapse. Both kidneys are tremendously enlarged and she suffers considerably from lumbar and hypochondriac discomfort. Nevertheless, her general health remains fairly good.

The patient with pyonephrosis was referred for an opinion by a general surgeon, who proposed to do a hysterectomy for fibroid, but hesitated because there were "many pus cells in the urine." The patient had diurnal and nocturnal frequency, lumbar pain, urgency of urination, and fever. I persuaded the doctor to do a nephrectomy and defer the contemplated hysterectomy.

The patient who had a papilloma of the bladder mentioned "bladder irritability" while suffering from acute appendicitis. After the appendectomy, frequency, urgency, and tenesmus still persisted. Cystoscopy disclosed the bladder tumor, which was removed by fulguration.

A relaxed vesical sphincter was found in several of the patients previously mentioned, but in one case was not associated with any other lesion of the urinary tract. This patient's impaired control was corrected by a Kelly operation on the vesical neck.

The patient who had carcinoma of the bladder suffered from an advanced carcinoma of the uterus, and lived but a short time after coming under observation. She had frequency, urgency, and hematuria.

In only a little more than 11 per cent of the 119 patients with urinary symptoms were the symptoms due entirely to lesions of the pelvic organs. The lesions in these cases were:

Fibromyoma of the uterus		6
Corpus	5	
Cervix	1	
Post-operative anteversion, with immobilization		2
Ovarian cyst		1
Pyosalpinx		1
Ectopic gestation		1
Varicosities—broad ligaments		1
Bartholinitis		1
Chancroids		1
Total		14

In every instance the urine was clear and free from pathogenic microorganisms. All these patients had coincident pelvic symptoms, except the two with postoperative anteversion of the uterus.

All six patients with fibromyoma of the uterus complained of fre-

quency of urination, but in only two did it cause nocturnal annoyance. In two others urgency was marked, and in another two there was suprapubic discomfort. The tumors were all intramural or subperitoneal, and quite large. Cystoscopy showed extravesical pressure and consequent distortion of the bladder wall in every case. One patient with a fat abdominal wall had been treated for six months by her physician for frequency and urgency of urination; her doctor did not suspect the presence of a tumor, as she had no other symptoms. Cystoscopy alone was sufficient to establish the diagnosis; there was a very marked bulging and distortion of the posterior wall of the bladder, without any evidence of cystitis.

The two patients with an extremely anteverted, almost immobilized uterus complained of frequency of urination only. They had both been operated upon for correction of retroversion, and were victims of operative "technic," at the expense of restoration of function. I could not determine what special technic had been followed, however. An extremely anteverted fundus, which cannot move backward to any extent as the bladder fills, causes extravesical pressure, capillary stasis, and serves as a constant irritant to the bladder in the course of time. This point should be borne in mind by gynecologic operators. Immobilization of an anteverted uterus is just as bad as a mobilized retroverted organ.

The large ovarian cyst, pyosalpinx, and ectopic pregnancy also excited frequency of urination through extravesical pressure.

In the patient with varicose veins of the broad ligament cystoscopy showed the same sort of varicosities in the bladder wall. Frequency of urination promptly disappeared after the incidental retroversion and broad ligament varicosities were cured by operation.

One woman with Bartholinitis complained of urethral pain, but had no specific urethral infection. This symptom was due to the pressure of a huge abscess, exerted on the urethra.

The patient with chancroids complained of burning on voiding, due to contact of the urine with the vulvar and perineal lesions.

It is interesting to note that ten patients had urinary symptoms for which no local cause could be found in either the pelvic organs or urinary tract. They were ascribed to the following extraneous causes:

Endocrine derangements	4
Neurasthenia	2
Neurosis	2
Circulatory hypertension	1
Menopause	1
Total	10

As is usually the case in disturbances of the internal secretory glands, there was definite indication of dysfunction of more than one

gland in three of the four cases. But it is significant that all exhibited several manifestations of hyperthyroidism. They all had increased frequency of urination, and three had impaired control.

One patient with neurasthenia had diurnal frequency; the other had urgency, without increased frequency. An obscure neurosis was blamed for two cases of nocturnal enuresis; one in a fourteen year old girl and one in an adult. These four patients were referred to a neurologist.

The woman with circulatory hypertension (systolic blood pressure 214) had diurnal and nocturnal frequency, both of which disappeared with the reduction of the abnormal pressure.

Similar symptoms occurring in another woman during her climacterium cleared up simultaneously with the hot flushes, sweats, and other menopausal manifestations, after the administration of ovarian and corpus luteum extracts.

CONCLUSIONS

While it is obvious that an exhaustive exposition of the several topics considered has not been attempted, and that the number of case records included in this study is not very large, I believe that sufficient evidence has been presented to justify the following conclusions:

1. A study of 600 consecutive private case records indicates that approximately 20 per cent of gynecologic patients will require a cystoscopic examination to establish a diagnosis.

2. About 15 per cent of gynecologic patients have some definite lesion of the urinary tract.

3. Many patients are deprived of prompt relief from symptoms because so many practitioners are willing to treat a woman for "cystitis," without actually demonstrating an inflammation of the bladder.

4. It is imperative for the gynecologist to have a working knowledge of cystoscopy.

5. All gynecologic patients should be catheterized on their first visit.

6. Valuable information can be obtained by the inspection of freshly catheterized urine.

7. A renal function test should be done before most elective gynecologic operations.

8. Pyelitis occurs frequently in women, and is often overlooked.

9. Fever is conspicuous by its absence in all cases of inflammation limited to the bladder.

10. In a small proportion of cases only urinary symptoms are caused by pelvic lesions, without coincident disease of the urinary tract.

11. Cases are encountered occasionally in which the urinary

symptoms are due to causes remote from the urinary and pelvic organs.

12. No urinary symptom, or symptom-complex, is pathognomonic of anything. The diagnosis rests almost entirely upon the objective evidence.

580 Park Avenue.

REPORT OF A CASE OF SOLID CARCINOMA OF THE OVARIES REACHING TO THE NAVEL, IN GIRL OF NINETEEN*

By Robert L. Dickinson, M.D., New York

THE family history and general health excellent, nervous balance perfect, intelligence high and athletic development such that she carried on her horseback hurdle jumping up to the time of her first visit. No disturbance of periods, no pain or discomfort or sense of pressure, no weight-loss; regular bowel action. First intimation of trouble was in mid-August, when, after an automobile accident, brief distress was located low in right side of the abdomen with mild temperature two days.

First seen Sept. 22, 1922, all general tests normal, remarkable poise and vigor. Tumor, smooth and with feel of fibroid, rising to height of navel on the right side, laterally from right crest to line half way between navel and left crest, mass filling pelvis snugly and on pelvic floor; beneath, very nodular and hard, and here strongly suggestive of malignancy. Diagnosis, double ovarian cyst, multilocular; fibroid or malignancy possible.

Operation at Brooklyn Hospital, Sept. 27. A little bloody ascitic fluid, no adhesions, no peritoneal involvement. Mass springs from right pelvic wall with ¾ turn of pedicle. Pelvis so filled as to mould the tumor on sacrum and pubes. With gentlest handling removed very close to pelvic wall; also uterus, (save for tip of cervix) tubes and most of broad ligaments. Other ovary has small growth; lymph glands not affected. No evidence of being secondary to cancer of stomach, gall bladder or bowel. Tumors solid, nowhere cystic, nowhere softened, judged by appearance malignant. Veins of short pedicle very large. Appendix removed. See diagrams.

Smooth convalescence. Upper two figure-eight silkworms slow to loosen with a little pus about them.

The measurements of the larger tumor were 8 x 4 x 4 inches, the abdominal portion relatively smooth and hard as a fibroid, the intrapelvic portion nodular and suggestive of malignancy. On section the surface did not have the appearance or feel of a fibroid, but it was smooth and slippery; to the eye there was no reticulated structure and the color was yellowish pink and not the white pink of a fibroid. The diagram shows where there were two rather bright yellow spots of the prevailing firmness, one one-third inch and one one-half inch in diameter. There were no cystic areas and nothing suggesting normal ovary. The left ovary is 1½" long by 1" thick and carries a band of finely granular pink surface across its equator which to the naked eye is suggestive of sarcoma. On section the portion next the broad ligament appears merely edematous. The remainder looks like the large tumor. The uterus is normal in size and the tubes and broad ligament normal, except for a few peritoneal cysts.

Pathologists' Report (Dr. C. V. Coulter).—A large tumor mass, uniform in appearance, of a fawn color, firm and cartilaginous consistency, containing caseous

*Presented at a meeting of the New York Obstetrical Society, December 11, 1923.

areas one centimeter or more in diameter. The small tumor in the opposite ovary has the same general appearance on section. It has no caseous area.

There is an abundant, dense, fibrous stroma, supporting closely-set solid alveoli and narrow infiltrating strands of tumor cells. Occasional gland formation is seen. The cells are of epithelial type.

These findings were confirmed by Professor Archibald Murray and the specimen preserved in the Museum of Long Island College Hospital.

A further report by Dr. Francis C. Wood states that the sections "show diffuse, small cell carcinoma involving apparently all the tissue submitted, so that it is not possible to recognize any normal structures. The walls of the vessels in some portions of this material are already invaded by the cells of the neoplasm. The prognosis in any case must be extremely bad."

Fig. 1.—Section of solid carcinoma of ovary in girl of nineteen (19) reaching to the navel and nearly filling the pelvis. (2/5 life size.) The left ovary is shown at the right in profile and in face.

On her return to town two months later there was found attached to the right wall of the true pelvis just below the brim (where the top of the broad ligament had been, a hard mass one-half the size of a plum). A week later Dr. R. E. Herendeen gave her a series of x-ray treatments. These did not cause the slightest physical or mental disturbance. This small mass disappeared. Eleven months after operation rectoabdominal examination shows that there is nothing in the pelvis save a barely recognizable, flexible string of scar leading upward each side from the little button of the vaginal portion of the cervix that was left. Liver, lungs and glands normal. Weight stationary. Fine general condition. No flushes or menopause disturbance.

At this writing, May 21, 1924, her general condition is the same and there are no local symptoms and no resistances in the lower abdomen.

59 East Fifty-fourth Street.

REPORT OF A CASE OF KRUKENBERG TUMOR*

By Onslow A. Gordon, Jr., M.D., Brooklyn, N. Y.

THE most extensive review recently on the subject of Krukenberg tumor is the work of Major in 1918. A review of the literature up to that time showed fifty-five definite cases. Because of the infrequency of this type of tumor, I desire to record this case of bilateral ovarian Krukenberg tumor (carcinosarcoma mucocellulare ovarii bilaterae secondarium) from the service of Dr. F. C. Holden at Bellevue Hospital.

The patient, a negress thirty-nine years of age, was first admitted May 9, 1922, complaining of a gradually increasing amenorrhea and slight pain in the lower ab-

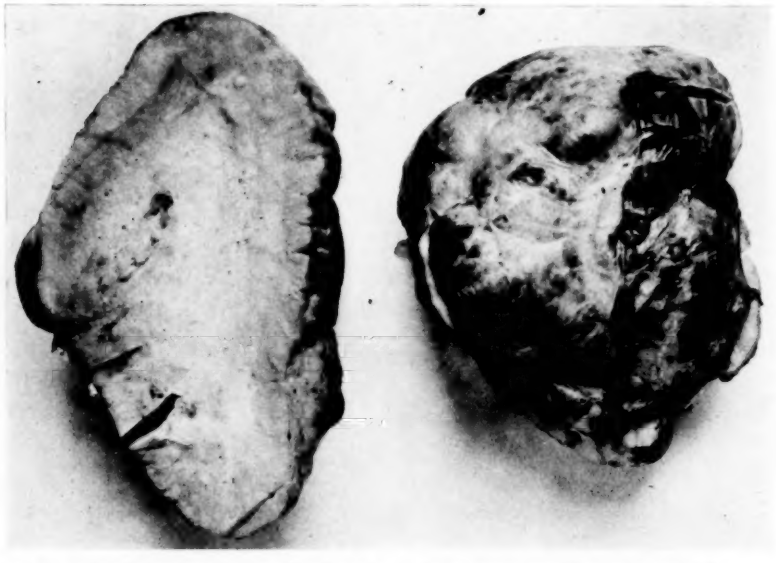

Fig. 1.—Showing the entire right ovary and a cross section of the left ovary.

domen. Her amenorrhea had been absolute for four months prior to admission. No mention was made of gastrointestinal symptoms at this time. Physical examination showed plainly palpable, hard, bilateral, pelvic masses. A preoperative diagnosis of bilateral ovarian fibromata was made.

A laparotomy was performed and the bilateral tumors which I will describe were easily removed. There was a moderate amount of clear fluid in the peritoneal cavity. A careful examination of the stomach and intestinal tract was not made at this time as the tumors were thought to be bilateral fibromata.

Macroscopic.—Bilateral ovarian tumors of approximately oval shape and equal size, each measuring approximately 16 centimeters in length by 11 centimeters

*Presented to the New York Obstetrical Society, December 11, 1923.

diameter, surface smooth, shows slight elevations and depressions. The tumors on section show a whitish gray solid structure which is largely hard with occasional softer, small cystic areas, none of them exceeding a few millimeters in size.

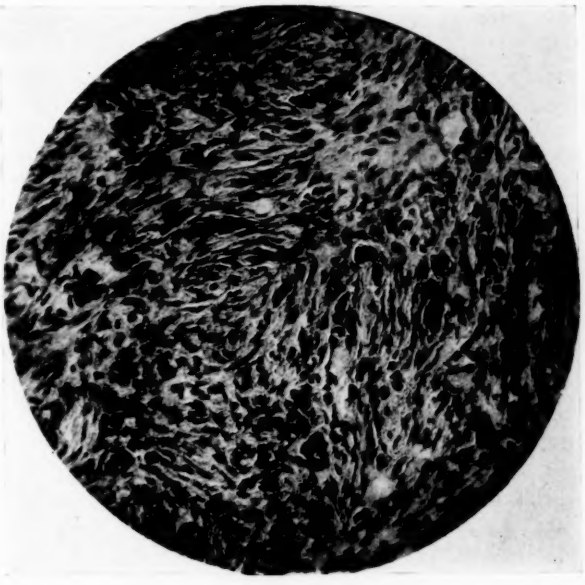

Fig. 2.—Showing the masses of spindle cells and so-called signet ring cells.

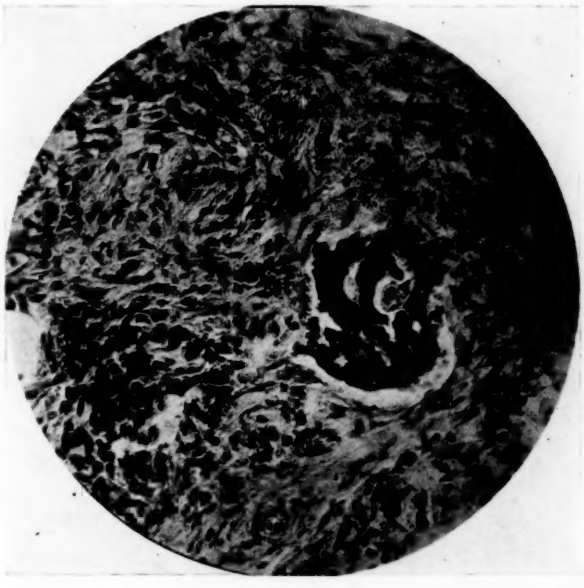

Fig. 3.—Showing whorls of spindle cells and a definite coil of epithelial cell type.

Microscopic.—Sections from the ovarian tumor show the entire ovarian tissue, with the exception of remnants of albuginea, replaced by a dense growth composed of masses of spindle cells with numerous mitotic nuclei. These spindle cells are

arranged in whorls, in certain portions, they contain large pale nuclei. In some places, outgrowing the number of spindle cells, one finds irregular and large hyperchromatic cells which fuse into giant cells or penetrate individually or in cell rows. Small circular lumina are lined with flattened cells of this type and near the edematous portion one finds large round cells with flat nuclei at the periphery, signet ring cells. A few wide tissue spaces are filled with coils of an epithelial cell type.

The patient made an uneventful recovery following her first operation and left the hospital one month after admission. At no time were definite gastrointestinal symptoms noted.

Three months after her first admission, she was readmitted complaining of nausea and vomiting and loss of weight. A second laparotomy, exploratory in character, was performed and a carcinoma of the pylorus was noted, thus establishing the primary location. The patient died one month after her second operation, but autopsy could not be obtained.

My case presents the usual clinical and pathologic features of this unusual type of tumor. The patient was thirty-nine years of age; Chapman found the average age to be thirty-six. The larger number of Krukenberg cases present symptoms of the primary location earlier than in our case. The tumor in the majority of the cases is secondary to the carcinoma of stomach or intestine and in 90 per cent of the cases is bilateral. All authenticated cases where the later course was known died of the disease.

71 Halsey Street.

Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D., Associate Editor

Collective Review

PROGRESS IN THE RELIEF OF STERILITY*

A Consideration of Developments in the Pathology, Bacteriology and Surgery of the Female Genitalia which Lead to a More Hopeful Prognosis

By Arthur H. Curtis, M.D., Chicago, Ill.

IT HAS long been accepted that at least 12 per cent of marriages are sterile and that gonorrheal infection is the predominating factor in the causation of sterility. Among the medical profession there has also been universal acceptance of the belief that surgical intervention, subsequent to infection, affords relief from sterility in only a small percentage of selected cases.

Recent advances in our knowledge and management of pelvic diseases have now materially changed the outlook. It therefore appears desirable to make a survey of the more important developments in this field which promise to improve the prognosis.

The limitations of our subject permit only passing consideration of sterility as it exists in the male. The husband's greatest influence in this trouble probably lies in the transmission of infection rather than in lack of the power to produce offspring. Aside from easily demonstrable congenital defects he is usually capable of procreation unless there has been a complicated gonorrheal infection or, more rarely, mumps or tuberculosis with associated involvement of the genitalia.

ABNORMAL PHYSIOLOGY IN RELATION TO STERILITY

As introductory to a consideration of physiologic disturbances in their bearing on sterility I wish to briefly emphasize two often unsuspected pathologic conditions which must be differentiated from physiologic disturbances. The first is gonorrhea, the second, mumps. As the result of study devoted to laboratory and clinical investigation of female pelvic infections, I am convinced that the gonococcus remains viable in the male genital tract much longer than genitourinary specialists are inclined to believe. Among the highest type of married women who complain of sterility we repeatedly find stigmata of former gonorrheal disease contracted from husbands who had been without symptoms for some years previous to marriage. It must

*From the Pathologic Laboratory and Gynecologic Service of St. Luke's Hospital. Annual Address to the Junior Students of Northwestern University Medical School.

ultimately be recognized that every man who has suffered from protracted gonorrheal infection requires painstaking eradication of residual foci, followed by an interval of years of rest before marriage is advisable.

Mumps infection is less important. There is, however, a considerable incidence of sterility among men who have had this disease with complicating scrotal involvement. Every young man who has suffered from mumps with orchitis should know that it is desirable to have a sperm test if matrimony is contemplated.

Turning now to purely physiologic problems in relation to sterility, the work of Reynolds and Macomber is of interest. They have arrived at particularly important conclusions concerning the relationship of mating to the bearing of young. Laboratory work leads them to the belief that apparently healthy individuals differ widely in reproductive power; a person low in the reproductive scale may succeed in obtaining offspring when mated with one possessed of high fertility, but when paired with an individual of average or deficient reproductive power there is much poorer prospect of pregnancy.

From a study of diets, Reynolds and Macomber found that calcium deficiency is an important cause of sterility and premature labor. Plenty of milk supplies this deficiency. If milk is objectionable, calcium lactate, gr. xx, t.i.d., may be employed. Lack of proper protein food, although important, is much less frequently responsible for sterility.

Conditions which influence the viability of spermatozoa in vaginal secretions have been extensively discussed. Little scientific information is available, however, aside from the fact that otherwise normal vaginal secretions are sometimes sufficiently acid to prevent conception. It is also demonstrable, clinically, that certain spermatozoa perish in secretions which are apparently normal in all respects. The administration of alkalies by mouth, e.g., sodium citrate, gr. xx, q.i.d., combats excessive vaginal acidity and, in practice, appears to exert a favorable influence in promoting pregnancy. Weakly alkaline low-pressure douches, occasionally administered before intercourse, may also be employed, but we must remember that douches are not entirely harmless. Within a year I have attended two patients who developed pelvic peritonitis subsequent to the use of high-pressure douches. Neither of these had previous external genital infection and in both instances examination revealed a patulous cervix; some of the douche fluid probably entered the open cervical canal and passed through the uterus and tubes directly into the peritoneal cavity.

Clinically interwoven with the problem of incompatability of genital secretions is that of sterility ascribed to temperamental incompatability of husband and wife. It is to be recognized that woman's receptiveness materially influences the character of the vaginal secretion and perhaps induces more frequent ovulation. But it is my belief that sterility among mismated couples more commonly results from various other causes, such as avoidance of conjugal relations, secretly employed contraceptive measures and other kindred procedures, not excluding unsuspected trips to the abortionist.

Pregnancy among mammals naturally recurs at yearly intervals.

Adaptation to assure survival of the species has brought about greater frequency among certain lower animals; many human beings, on the contrary, have achieved a modification in the other direction. Although it is now normal for the average educated woman of this country to conceive somewhat irregularly, there remains a tendency to the establishment of a two-year or three-year cycle. Provided that husband and wife both give a history of good health, critical examination reveals no infection, and viable healthy spermatozoa are obtained, a diagnosis of relative sterility is warranted only after the expiration of a period of three years. Until these three years have elapsed treatment should be limited to simple measures.

It is worthy of note that sexual indulgence at infrequent intervals increases the likelihood of pregnancy. The most auspicious time is probably immediately following the cessation of menstruation. Most women then have greater desire and the cervical canal is widely open for entrance of spermatozoa. Also, it is known that ovulation occurs shortly after menstruation and viable spermatozoa should at this time have maximum prospects of reaching the ovum. It is worthy of note that spermatozoa have been recovered from women as much as ten days after coitus.

In the event of otherwise unaccountable sterility, insemination has been strongly advocated. We have met with failure in the few instances in which it has been attempted and have feared that this procedure introduces considerable danger of infection.

THE BODY OF THE UTERUS IN RELATION TO STERILITY

Chronic infections of the endometrium are now known to be uncommon and the old belief that "chronic endometritis" is a cause of sterility is now untenable. We have learned that curettage does not cure sterility, but is helpful mainly because it is accompanied by dilation of the cervix which relieves obstruction of the canal.

Some years ago we obtained evidence of considerable interest relative to the dangers of curettage. In certain cases normal scrapings were obtained from the uterus; then, several days thereafter, in the endometrium secured by hysterectomy, mixed cultures and endometritis were found. Clinical observation reveals a frequent incidence of sterility among otherwise healthy patients who have been curetted, after spontaneous abortion, for the purpose of "cleaning out" the uterus. It is apparently difficult to curette a bleeding uterus without danger of introducing low-grade infection. The essential pathology in such cases probably is an inflammation which encroaches upon the lumen of the interstitial portion of the fallopian tubes.

Uncomplicated displacements, although a predisposing cause of abortion, seem not to greatly interfere with conception. Fibroid tumors, on the contrary, often appear to mechanically interfere with conception as well as with the development of the fetus in case pregnancy does occur.

From the foregoing it is evident that treatment of the body of the uterus, aside from removal of tumors, seems to offer little help in the promotion of pregnancy. This statement does not, of course, cover the problems of abortion and premature labor; in these it is certain that uterine displacements, syphilis and focal infections play a large part.

THE CERVIX IN RELATION TO STERILITY

In consideration of the cervix one need scarcely mention that sterility is often relieved by thorough dilation, especially in the presence of marked congenital anteflexion.

Gross lesions of the cervix, notably those with associated purulent leucorrhea, play an important part in the prevention of conception. We believe that purulent leucorrhea has origin chiefly in small glands about the urethra and in hyperplastic hypersecreting infected glands of the cervix. Procedures directed toward cure of this condition often necessitate destruction or removal of all of the cervical mucosa up to the level of the internal os. At other times the only pathology may be a torn, everted, enlarged anterior lip with a constantly reforming mucous plug in the canal. A few moments' repair work may suffice to bring about relief.

Occasionally a congenitally short anterior vaginal wall tilts the cervix forward to such a degree that spermatozoa cannot enter. This condition is easily overlooked at the time of examination. When recognized, relaxation is obtained through a simple plastic operation. Anterior cervical displacements from other causes seldom produce sterility because they tend to be less constantly present, and, even if persistent, the supports of the cervix usually permit it to hang low enough for the entrance of spermatozoa.

During the last three years, I have been increasingly impressed by the helpfulness of cervical operations in bringing about relief from sterility, notably if these lesions are accompanied by purulent leucorrhea. Within six weeks we have delivered babies from two previously sterile women of this type and now have under observation a third patient who is three months pregnant. All of these women became pregnant within two months after leaving the hospital. It is obvious that treatment should not be attempted without first determining that the husband is healthy and that the fallopian tubes are patent.

THE FALLOPIAN TUBES IN RELATION TO STERILITY

(a) *Gonorrheal infection of the tubes* stands out as the one great cause of sterility and it is desirable that we consider certain recently noted characteristics of this disease which have a direct bearing upon sterility problems. In a large series of cases, cultivation of the entire tube, after thorough grinding, has revealed that infection rarely persists longer than two weeks subsequent to the disappearance of fever and leucocytosis. We assume, then, that gonorrheal salpingitis is a rather quickly self-limited disease. We have also been able to demonstrate that the body of the uterus does not harbor chronic gonorrheal infection. So-called "chronic gonorrheal salpingitis" therefore appears to be a reinfection of the tubes with fresh organisms from an outside source or from the chronically diseased lower genital tract.

Acting upon this laboratory evidence we have noted clinically that patients who have greatly thickened chronically diseased tubes of gonorrheal origin usually belong to the prostitute class or have freely cohabited with chronic carriers of infection. On the contrary, patients who are early isolated from the source of their disease usually bear a single attack of salpingitis without protracted clinical symptoms or severe pathologic results.

The mucosa of the tube is the part first invaded and ultimately most crippled, although severe gonorrheal infection tends to involve the entire thickness of the tube. Even after slight infection, healing is accompanied by microscopic adhesions between the folds of the mucous membrane. In more severe cases gland-like pockets of distorted mucosa also extend deeply into the wall of the tube. Therefore, although the fimbriae may remain open and the lumen patent, the ovum must travel along a difficult path provided with rough surfaces and pockets which interfere with fertilization and predispose to the development of tubal pregnancy.

A further point of pathologic interest is this: if operative relief is attempted in patients who have previously had salpingitis it is well to know that gonorrheal pelvic adhesions, even though numerous and dense, are always amenable to separation by blunt dissection.

(b) *Tubal infection after abortion.*—Sterility subsequent to abortion occurs very frequently. Most often there has been instrumental interruption of pregnancy. Less frequent, but perhaps more in need of consideration, is sterility which occurs in patients who have spontaneously aborted and thereafter have been curretted.

It has long been known that infection which complicates abortion travels through the cellular tissues rather than along the mucous membranes. The tubes, if diseased, present only part of a relatively diffuse process. We have learned that the tubes when involved, are usually attacked from without, the infection producing a perisalpingitis, with tendency to invasion of the mucosa last, if at all. From the viewpoint of relief of sterility this means that if other pathology is corrected the ovum has better prospects of free passage along the tube lumen than after gonorrheal disease of equal severity.

Other factors, however, make the prognosis less favorable after postabortive infection. For example, streptococci are the invading organisms in most instances, and these bacteria, in contrast with the gonococcus, may remain viable in the tisuses for many years after subsidence of the infection. Through cultivation of the ground tissues I have isolated the streptococcus even as long as eighteen years subsequent to the introduction of the disease.

Another unavoidable possibility is that of postabortive infection of the uterine wall in that region traversed by the fallopian tubes. Especially if the infected uterus has been curetted there is danger of interstitial tubal obstruction. Thanks to Rubin, we now possess a means of testing the patency of fallopian tubes. The technic of this procedure is easily mastered, the danger of introducing infection is slight, and the information thus obtained is of great value. It is also to be anticipated that transuterine inflation of the tubes will prove to be of therapeutic value in the relief of sterility.

c) *Relief of sterility after tubal disease.*—The trend of my clinical and laboratory work has led to a marked change in my views relative to two surgical problems. I have become a warm advocate of operation for relief of lower abdominal adhesions and am more favorably impressed by the feasibility of obtaining operative relief from sterility in carefully selected cases. These two subjects are closely related; firstly, because patients with sterility often suffer from pelvic adhesions, and secondly, because delicate surgical technic is necessary for relief of both.

Certain conditions and indications for attempted operative interference merit brief consideration:

The husband must be normal, without suspicion of residual infection.

The patient should be relatively free from purulent leucorrhea and cervical pathology.

The Rubin test should demonstrate occlusion of the fallopian tubes. We must not forget that reestablishment of tubal patency sometimes follows this test, and in selected cases the patient should be given ample time to become pregnant.

The etiology of the pathologic changes materially influences the prognosis. Sterility after mild postabortive infection is most favorable of all. In severe infections, however, the streptococcus has a long period of viability in the tissues, which makes us wary of early surgery. In such instances interference should be postponed for a minimum of two years.

The preoperative prognosis in patients who have had a brief attack of gonorrheal salpingitis is favorable. Repeated attacks make the outlook unfavorable. Likewise, if the husband had gleet or other persistent infection at the time of marriage there is prospect that the tubes are hopelessly crippled from recurrent infections, even though the patient has been relatively free from symptoms.

Inflammatory pelvic masses of sufficient size to be readily palpated make the prognosis distinctly unfavorable.

At operation, avoidance of hurry is imperative. It is usually possible to employ blunt dissection, with the scissors, along natural lines of cleavage. Rubber pads leave free surfaces whereas gauze packing produces fresh adhesions. Ligated tissues should be cut close to the point of ligature; we have demonstrated in animals that pedicles of considerable length become necrotic and adhere to adjacent surfaces. This plan of cutting close makes necessary the use of suture-ligatures whenever the pedicle is sufficiently large to permit the retraction of vessels. The value of absolute hemostasis and the helpfulness of omental transplants to cover raw surfaces require no comment.

Air distention of the fallopian tubes from within the abdomen at the time of operation is very helpful. The air is introduced from a Luer syringe held at the fimbriated extremity and is then milked along the tube in the direction of the uterus. In case of occlusion there is absence of a characteristic gurgle, always to be heard when there is free passage into the uterine cavity. This procedure makes possible a visual determination of the patency of grossly normal or doubtful tubes; strictures are localized and their extent determined; the interstitial portion of the tube becomes accessible, a factor of notable value after postabortive metritis; pressure upon the column of air irons out the mucosa, obliterating pockets between adjacent folds of the mucous membranes; distention of the tube also magnifies anatomic relationships, revealing congenital anomalies and membranous bands which interfere with normal function.

CONCLUSIONS

1. Provided that husband and wife both give a history of good health, critical examination reveals no infection, and viable healthy spermatozoa are obtained, a diagnosis of relative sterility is warranted only after the expiration of a period of three years. Until

these three years have elapsed treatment should be limited to simple measures.

2. Although sterility is sometimes ascribable to general ill health, improperly balanced diet, unsatisfactory mating, or abnormalities of genital secretions, it is probable that these various physiologic disturbances are the sole cause of sterility in only a small percentage of cases.

3. Gonorrheal infection and infection after abortion are the outstanding causes of sterility.

4. The gonococcus probably remains viable in the male genital tract much longer than has been believed; this is indicated by the frequent presence of stigmata of former gonorrheal disease among sterile married women whose husbands had been pronounced cured a considerable time previous to marriage.

5. Histologic and bacteriologic study of uteri removed several days after curettage showed that this procedure tends to introduce infection. Clinical observation reveals a frequent incidence of sterility among otherwise healthy patients who have been curetted, notably after abortion, for the purpose of "cleaning out" the uterus.

6. In the absence of other pathology, relief of abnormal conditions of the cervix is often followed by pregnancy; this is notably true if there is congenital obstruction of the canal or cervicitis with associated purulent leucorrhea.

7. Treatment of the body of the uterus seems to exert slight influence in the promotion of conception.

8. Operative interference, for relief of sterility resultant from tubal disease, yields much more satisfactory results than were formerly obtained; operation should be limited to selected cases which have been subjected to special preoperative study.

104 South Michigan Ave.

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Item

At the Annual Meeting of the American Gynecological Society held at Hot Springs, Virginia, May 15, 1924, the following officers were elected for the ensuing year:

President, Dr. Howard C. Taylor, 32 W. 50th Street, New York City; *1st Vice-President,* Dr. Franklin S. Newell, 443 Beacon Street, Boston, Mass.; *2nd Vice-President,* Dr. Frederick J. Taussig, 3519 Washington Ave., St. Louis, Mo.; *Secretary,* Dr. Arthur H. Curtis, 104 S. Michigan Ave., Chicago, Ill.; *Treasurer,* Dr. Charles C. Norris, 22nd and Chestnut Sts., Philadelphia, Pa. Other Members of the Council: Dr. Walter William Chipman, Montreal, Canada; Dr. George Gray Ward, New York City; Dr. John A. Sampson, Albany, N. Y.; Dr. Barton Cooke Hirst, Philadelphia, Pa.; Dr. Edward A. Schumann, Philadelphia, Pa.; Dr. William S. Stone, New York City.